REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

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1. REPORT DATE *(DD-MM-YYYY)*	2. REPORT TYPE	3. DATES COVERED *(From - To)*
2012	Book Chapter-Wilderness Medicine Textbook	

4. TITLE AND SUBTITLE

Pathophysiology of Heat-Related Illnesses

5a. CONTRACT NUMBER

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Thermal and Mountain Medicine Division
U.S. Army Research Institute of Environmental Medicine
Natick, MA 01760-5007

8. PERFORMING ORGANIZATION REPORT NUMBER

MISC 10-37

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)

Same as #7 above.

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION/AVAILABILITY STATEMENT

Approved for public release; distribution unlimited.

13. SUPPLEMENTARY NOTES

14. ABSTRACT

Heat illnesses are best viewed as existing along a continuum, transitioning from the mild conditions of heat cramps and heat exhaustion to the life-threatening condition of heatstroke. Environmental heat exposure is one of the most deadly natural hazards in the United States, with approximately 200 heatstroke deaths per year. Although the majority of heatstroke deaths are observed in vulnerable populations during annual heat waves, young fit individuals may also succumb to heatstroke while engaging in strenuous activities such as athletic competitions, military operations, or occupational tasks. Multiorgan system failure is the ultimate cause of heatstroke death, and there is complex interplay among the physiologic and environmental factors that compromise an individuals' ability to adequately respond to heat stress. The pathophysiology of heatstroke is thought to be caused by a systemic inflammatory response that occurs in response to endotoxin leakage from the gut, but there remains limited understanding of the mechanisms that mediate morbidity and mortality. This chapter provides an overview of the pathophysiologic responses that are observed in patients

15. SUBJECT TERMS

heat illness, heatstroke, endotoxin

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			L.R. Leon
Unclassified	Unclassified	Unclassified	Unclassified	27	19b. TELEPHONE NUMBER *(Include area code)* 508-233-4862

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vaginal candidiasis, menstrual problems, and urinary tract infections.

THE USE OF FROZEN MEDICATIONS

The medical literature is relatively sparse on this topic.[31] One of the authors has rewarmed frozen fluorescein stain, oxybuprocaine hydrochloride 0.4%, ophthalmic local anesthetic, corticosteroid creams, antifungal creams, inhaled salbutamol, and IV hydrocortisone, all of which worked normally after rewarming. All forms of tablet medication warmed from frozen have also been fine after rewarming. A study from the BAS found that most medications remained stable, even after multiple freeze-thaw cycles. The exception was hydrocortisone cream, although the investigator also recommended against subjecting eye medications to temperature extremes.[F] Medical devices, such as IV cannulas, worked normally after rewarming, as did all forms of tape and dressings. Frozen IV fluids expanded when frozen, perforated the bags, and thus leaked when rewarmed.

Acknowledgments. Special thanks to Kenneth H Willer, MLS, Manager—Library Services, Samaritan Health Services, Corvallis, Ore, kwiller@samhealth.org.

REFERENCES

Complete references used in this text are available online at www.expertconsult.com.

CHAPTER 10

Pathophysiology of Heat-Related Illnesses

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Heat illnesses are best viewed as existing along a continuum, transitioning from the mild conditions of heat cramps and heat exhaustion to the life-threatening condition of heatstroke. Environmental heat exposure is one of the most deadly natural hazards in the United States, with approximately 200 heatstroke deaths per year. Although the majority of heatstroke deaths are observed in vulnerable populations during annual heat waves, young fit individuals may also succumb to heatstroke while engaging in strenuous activities such as athletic competitions, military operations, or occupational tasks. Multiorgan system failure is the ultimate cause of heatstroke death, and there is complex interplay among the physiologic and environmental factors that compromise an individuals' ability to adequately respond to heat stress. The pathophysiology of heatstroke is thought to be caused by a systemic inflammatory response that occurs in response to endotoxin leakage from the gut, but there remains limited understanding of the mechanisms that mediate morbidity and mortality. This chapter provides an overview of the pathophysiologic responses that are observed in patients and experimental animal models at the time of heatstroke collapse and during long-term recovery. A brief discussion is provided on current clinical heatstroke treatments and promising avenues of research that may aid in the development of more effective interventions and/or treatments to prevent this debilitating illness.

Heat Stress and Thermoregulation

FOUR AVENUES OF HEAT EXCHANGE

Mammals and other homeotherms are capable of maintaining body temperature within a fairly narrow range (approximately 35°-41° C [95°-105.8° F]) despite large fluctuations in environmental temperature. Environmental variables that have the largest impact on heat exchange are temperature; humidity; radiation from the air, water, or land; and air or water motion.[88] To maintain stable body temperature, organisms rely on four avenues of heat exchange: conduction, convection, radiation, and evaporation.

Dry heat exchange is achieved by conduction, convection, and radiation. The effectiveness of these mechanisms depends on differences between the skin and environmental temperatures. That is, dry heat loss occurs when skin temperature exceeds that of the environment, and dry heat gain occurs when environmental temperature exceeds that of the body. Conduction occurs when the body surface is in direct contact with a solid object and depends on the thermal conductivity of the object and the amount of surface area in contact with the object. Conduction is typically an ineffective mechanism of heat exchange caused by behavioral adjustments that minimize contact with an object. For example, the wearing of shoes is an effective behavioral adjustment that minimizes conduction of heat from a hot surface (e.g., desert sand) to the foot. Within the body, conductive heat transfer occurs between tissues that are in direct contact with one another, but is limited by poor conductivity of the tissues. For example, subcutaneous fat has approximately 60% lower conductivity than does the dermis and impedes conductive heat loss.[332] Convection is a mechanism of dry heat transfer that occurs as air or water moves over the skin surface. The windchill index is an example of the convective cooling effect of wind velocity. The rate of convective heat transfer depends on the temperature gradient between the body and environment, thermal currents, bodily movements, and area of the body surface that is exposed to the environment, which can vary dramatically with different clothing ensembles. Within the body, convective heat transfer occurs between the blood vessels and tissues and is most efficient at the capillary beds, which are thin walled and provide a large surface area for heat exchange. Radiative heat transfer is electromagnetic energy that is exchanged between the body and surrounding environmental objects and is independent of air velocity or temperature. It is effective even when air temperature is below that of the body. All objects within our environment absorb and emit thermal radiation, but clothing can reduce the radiant heat that impinges on the skin from various environmental sources.

Evaporation represents a major avenue of heat loss when environmental temperatures are equal to or above skin temperature or when body temperature is increased by vigorous physical activity. In humans, evaporative cooling is achieved as sweat is

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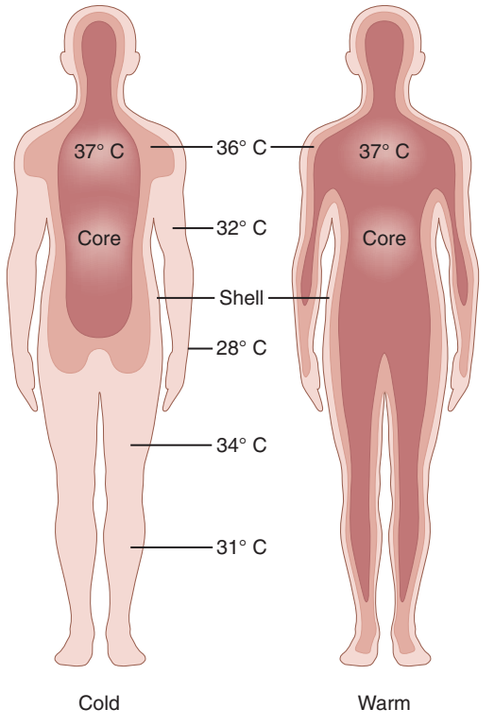

FIGURE 10-1 Distribution of temperatures within the human body into core and shell during exposure to cold and warm environments. The temperatures of the surface and the thickness of the shell depend on the environmental temperature: the shell is thicker in the cold and thinner in the heat. *(From Elizondo RS: In Rhoades RA, Pflanger RG, editors:* Human physiology, *ed 3. Philadelphia, 1996, Saunders College,. Reprinted with permission of Brooks/Cole, a division of Thomson Learning, http://www.thomsonrights.com.)*

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vaporized and removes heat from the skin surface, with approximately 580 kcal of heat lost per each liter of evaporated sweat.[94] The most important environmental variables affecting evaporative cooling are ambient humidity and wind velocity. Sweat is converted to water vapor and readily evaporates from the skin in dry air with wind, whereas the conversion of sweat to water vapor is limited in still or moist air. If sweat accumulates and fails to evaporate, sweat secretion is inhibited and the cooling benefit is negated. Small mammals, such as rodents, do not possess sweat glands but achieve evaporative cooling by grooming nonfurred and highly vascularized skin surfaces, such as the ears, paw pads, and tail with saliva that evaporates in a manner similar to that of sweat in humans.[104,294]

BODY TEMPERATURE CONTROL

Regulation of a relatively constant internal temperature is critical for normal physiologic functioning of tissues and cells because membrane fluidity, electrical conductance, and enzyme functions are most efficient within a narrow temperature range. By convention, thermal physiologists describe body temperature control with a two-compartment model that consists of an internal core (i.e., viscera and brain) and an outer shell (i.e., subcutaneous fat and skin) (Figure 10-1).[70]

The skin is the final barrier between the body and the environment and functions as a conductive pathway for heat transfer to the environment, while also serving as the primary site to sense changes in environmental temperature. Skin temperature may fluctuate because of changes in environmental temperature, relative humidity, wind velocity, and radiation. Heat-transfer mechanisms are evoked in response to changes in body heat storage (S), which depends on metabolic rate, work, and the four avenues of heat exchange, as follows:

$$S = M - (W) - (E) - (C) - (K) - (R)$$

where M is metabolic rate, W is work, and E, C, K, and R are evaporative, convective, conductive, and radiant heat transfer, respectively.[132] The impact of the four avenues of heat exchange on total body storage depends on a variety of organismal (e.g., age, sex, adiposity), environmental (e.g., humidity, wind velocity), and occupational (e.g., protective clothing, work intensity) variables. Under conditions in which heat production and/or heat gain exceeds heat loss, such as during exercise or heat exposure, positive heat storage occurs and body temperature increases. When heat loss exceeds heat production and/or heat gain, such as during prolonged cold exposure, negative heat storage occurs and body temperature decreases.[88]

Endothermic animals use both autonomic and behavioral thermoeffector mechanisms to regulate body temperature. Autonomic thermoeffector responses are often referred to as "involuntary" and include sweating, vasodilation, vasoconstriction, piloerection (furred mammals), and shivering and nonshivering thermogenesis (brown fat heat production). Behavioral thermoeffector mechanisms are considered "voluntary" and include clothing changes, use of heat or air conditioning systems, huddling or use of blankets, fan cooling, and seeking of shade or shelter. Rather than working independently of one another, autonomic and behavioral thermoeffector mechanisms typically function in concert to maintain temperature control. For example, evaporative cooling in rodents requires autonomic stimulation of salivation and behavioral spreading of saliva onto nonfurred surfaces.[104,294] Many large species in the wild use natural water sources to facilitate cooling. Elephants spray water onto their skin surface, and hippopotamuses and other species are often observed near or in watering holes. Water is a more effective medium to facilitate convective heat transfer than is air, because of its high heat-transfer coefficient (approximately 25 times greater than air),[305] even if the water temperature is tepid. However, voluntary suppression of behavioral mechanisms of cooling in humans can increase the risk for thermal injury. This is illustrated by older adults who refuse to use air conditioning systems or leave their residences during heat waves, or highly motivated athletes and military personnel that voluntarily dehydrate and/or sustain a high rate of work in hot weather.

Regulation of body temperature is best conceptualized as a negative-feedback system consisting of sensors, integrators, and effectors. In vertebrates, neurons in the skin, spinal cord, and abdomen sense thermal stimuli and convert those signals to action potentials that are transmitted by afferent sensory neurons to the preoptic area of the anterior hypothalamus (POAH). The POAH is considered the main central nervous system (CNS) site for thermoregulatory control because it receives and integrates synaptic afferent inputs and evokes corrective autonomic and behavioral thermoeffector responses for body temperature regulation.[28] A diagrammatic representation of this negative-feedback loop is shown in Figure 10-2.

The concept of a temperature set point was developed as a theoretical framework to examine regulated and unregulated changes in body temperature.[19] The temperature set point is analogous to a thermostat that controls a mechanical heating device; under homeostatic conditions, body temperature is approximately equal and oscillates around the temperature set point. Environmental perturbations, such as heat and exercise, cause body temperature to deviate from the set-point temperature as heat gain and/or production exceeds heat loss and the organism becomes hyperthermic (body temperature is greater than the set-point temperature). During prolonged cold exposure, heat loss exceeds heat gain and/or production and the organism becomes hypothermic (body temperature is less than the set-point temperature) (Figure 10-3).

Regulated increases and decreases in the temperature set point are referred to as fever and regulated hypothermia (also called anapyrexia), respectively, and are protective immune responses to infection, inflammation, or trauma. Fever is defined as a regulated increase in the temperature set point and is actively established and defended by heat-producing (e.g., shivering and nonshivering thermogenesis) and heat-conserving (e.g., peripheral vasoconstriction, huddling to reduce exposed body surface area) thermoeffectors (see Figure 10-3).[132] An individual is considered normothermic once fever is established and body

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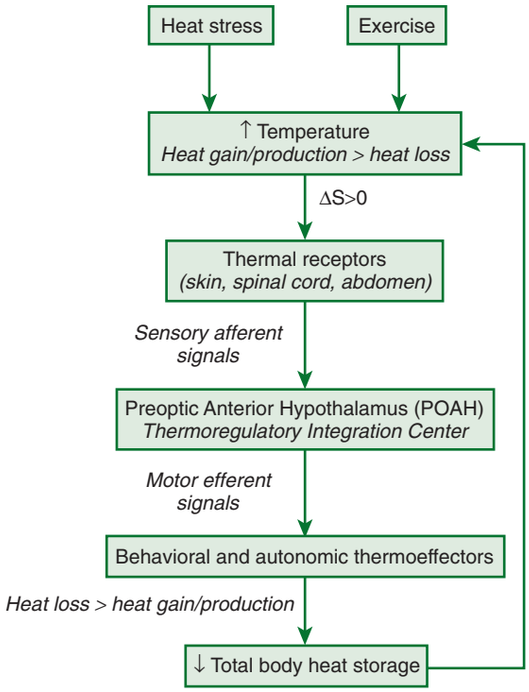

FIGURE 10-2 Diagrammatic representation of the negative feedback pathway regulating core temperature in homeotherms. Climatic heat stress and exercise (metabolic work) cause heat gain/heat production to exceed heat loss (ΔS > 0) and increase body temperature above baseline. The increase in total body heat storage is sensed by thermal receptors in the skin, spinal cord, and abdomen, which transmit action potentials via sensory afferent nerves to the preoptic area of the anterior hypothalamus (POAH). The POAH receives and integrates synaptic afferent inputs and evokes corrective behavioral (e.g., fanning, removal of clothing) and autonomic (e.g., vasodilation, sweating) thermoeffector responses to decrease total body heat storage and return body temperature to baseline. indicates stimulatory pathway, indicates inhibitory pathway.

temperature oscillates around the new elevated temperature set point (see Figure 10-3). The highly regulated nature of fever was first suggested by Liebermeister in the 1800s when it was observed that individuals actively reestablished an elevation in body temperature following experimental warming or cooling.[180,286] Fever is a protective immune response used by invertebrates, fish, amphibians, reptiles, and mammals to survive infection or injury.* The protective effects of fever are mediated by increased mobility and activity of white blood cells,[218,313] increased production of interferon (IFN; antiviral and antibacterial agent) antibodies[64], and reduced plasma iron concentrations, the effects of all of which inhibit the growth of pathogens.[89,156] In mammals, the inhibition of fever using antipyretic drugs (e.g., aspirin) increases mortality from bacterial and viral infection, which speaks to the importance of fever as an immune response.[126,315]

Many species also develop regulated hypothermia to survive severe environmental insults. Regulated hypothermia is elicited in response to a decrease in the temperature set point and is actively established and defended by behavioral and autonomic heat-loss mechanisms.[132] The Q_{10} effect states that each 10° C (18° F) change in body temperature is associated with a twofold to threefold change in enzymatic reaction rates. Based on this relationship, a regulated decrease in body temperature is thought to protect against injury and inflammation by reducing production of harmful enzymatic end products that compromise tissue function under conditions of low oxygen supply. In bumblebees, infected worker bees spend significantly more time in cooler temperatures outside of the nest than do healthy worker bees; this cold-seeking behavior is associated with increased survival from parasitic infection.[118,213] Mice inoculated with influenza virus also show cold-seeking behavior and develop regulated hypothermia, which is associated with improved infection outcome.[153] Other environmental insults that induce regulated hypothermia in small rodents include hypoglycemia,[34,98] hypoxia,[194,252] hemorrhage,[119] dehydration,[129] infection,[153,176,264] and heatstroke.[173,174]

*References 32, 54, 154, 216, 256, 316.

Mechanisms of Heat Dissipation During Thermal Stress

Cardiovascular mechanisms have evolved to shunt warm blood from the body core to the skin surface and increase heat loss during thermal stress. Arteriovenous anastomoses (AVAs) are collateral connections between adjacent blood vessels that increase the volume of blood that is delivered to a particular tissue. Mean skin blood flow can vary approximately 10-fold in humans depending on the thermal environment. The hands and feet are concentrated with AVAs that serve as effective areas for dry heat loss. The nonfurred surfaces of small rodents, such as the ears, tail, and paw pads, also have an abundance of AVAs and a large surface area to facilitate convective heat transfer.[92,99] During exercise heat stress, increased blood flow to the skin surface is accompanied by sweat secretion. The density, secretion rate, and activation threshold of regional sweat glands determine the volume of sweat loss at a body site. In humans, the back and chest have the highest sweat rates for a given body temperature change, whereas only approximately 25% of total sweat is produced by the lower limbs.[217] Additional factors affecting sweat

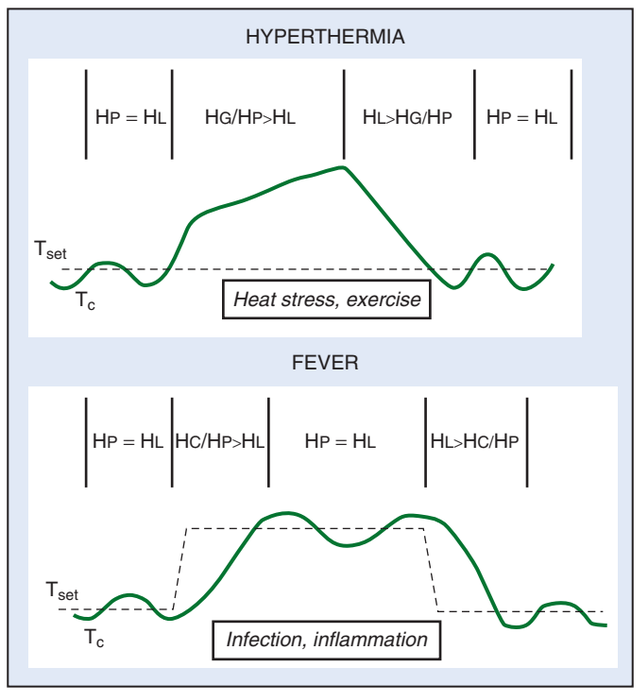

FIGURE 10-3 The theoretic concept of core temperature (T_c) changes mediated by a change in the temperature set point (T_{set}). Hyperthermia represents an increase in T_c in the absence of a change in T_{set}. In response to climatic heat stress, exercise, or the combination of these factors, heat gain (H_G) and/or heat production (H_P) exceed heat loss (H_L) and T_c rises above T_{set} as the organism becomes hyperthermic. In response to removal from the heat, cooling, or cessation of exercise, H_L exceeds H_G/H_P and T_c returns to baseline. Fever is defined as a regulated increase in body temperature that is actively established and defended by behavioral and autonomic thermoeffector responses that increase heat conservation (H_C) and/or H_G and decrease H_L to increase T_c to a new elevated level. The rising phase of fever is associated with shivering (increases H_P) and the donning of blankets (increases H_C). The individual feels "cold" until a new elevated level of T_c is attained. Note that while fever is maintained, T_c oscillates around T_{set} and the individual is considered normothermic with $H_P = H_L$. Once fever breaks, H_L exceeds H_C/H_P as the individual sweats, removes clothing, and so forth, to return T_c to the baseline level.

rate include clothing characteristics, environmental conditions, and rate of metabolic heat production. Panting is an effective method of evaporative heat dissipation in large animals, such as birds, dogs, sheep, and rabbits, and occurs at a resonant ventilation frequency that requires minimal energy expenditure.[107,257,329] Humans and rodents do not pant per se, but breathing frequency and minute volume increase during severe heat exposure to facilitate evaporative cooling from the respiratory surfaces. In humans, the contribution of respiratory evaporative cooling is small compared with skin evaporative cooling (Figure 10-4).

DEHYDRATION AND ELECTROLYTE IMBALANCE

Water requirements during heat exposure are primarily determined by a person's sweat losses. Water depletion dehydration develops when the rate of water replacement is not adequate, which can be a result of a mismatch between fluid intake and sweat loss, lack of water availability, or use of diuretic medications. Sweat rates may range from 0.3 to approximately 3 L/hr during athletic or occupational activities, depending on the environmental conditions and type, duration, and intensity of work.[47,143] If high sweat rates are maintained without adequate replenishment of lost water, this can cause electrolyte imbalances that impede the efficiency of autonomic mechanisms of thermoregulatory control. For example, hyperosmolarity alters heat responsiveness of warm-sensitive neurons in the POAH and limits the effectiveness of evaporative heat loss.[121,219,276] Severe hypernatremic dehydration is associated with brain edema, intracranial hemorrhage, hemorrhagic infarcts, and permanent brain damage (*Figure 10-5, online*).[214]

Severe reductions in electrolytes can have a profound impact on heatstroke outcome. Symptomatic hyponatremia (decreased serum sodium concentration) is a relatively rare condition, but it has been observed in marathon runners and military recruits during training exercises as a consequence of overconsumption of hypotonic fluids with inadequate replacement of sodium losses.[210,230] Intracellular swelling is a severe consequence of hyponatremia that may cause CNS dysfunction. Hypokalemia (decreased serum potassium concentration) may be caused by overproduction of aldosterone, excessive sweating, or respiratory alkalosis. Any cause of overproduction of urine (polyuria) potentially causes urinary potassium loss.[323] Potassium is a potent vasodilator of blood vessels to the skeletal and cardiac muscles, so excessive loss of this electrolyte can have detrimental effects, such as decreased sweat volume, cardiovascular instability, and reductions in muscle blood flow that predispose to skeletal muscle injury (i.e., rhabdomyolysis).[158,279]

Heat Illnesses

Heat illnesses are best viewed as existing along a continuum that transition from the mild conditions of heat cramps and heat exhaustion to more serious conditions of heat injury and heatstroke (Table 10-1).

Heat cramps are typically brief but can cause agonizing pain in the skeletal muscles of the limbs and trunk. Cramps may be recurrent but are typically confined to the skeletal muscles that are involved in vigorous exercise in the heat. Skeletal muscle spasms in the extremities may be sporadic, but they are painful and develop most frequently in persons who are not acclimatized to physical exertion. However, heat cramps may also occur in fit athletes who are salt depleted. Heat cramps do not predispose to more serious heat illness and are not associated with complications beyond muscle soreness. The cause of heat cramps is not fully understood, but cramps are thought to occur in response to increased intracellular calcium release that stimulates actin–myosin filaments and muscle contraction. Current treatments include rest and replacement of electrolytes with fluids or salted food. Salt tablets should be avoided because they can cause gastrointestinal irritation and may stimulate excess potassium loss in the distal tubules of the kidney.

Heat exhaustion (also referred to as heat prostration or heat collapse) is a mild to moderate form of heat illness that is associated with moderate (>38.5° C [101.3° F]) to high (>40° C [104°

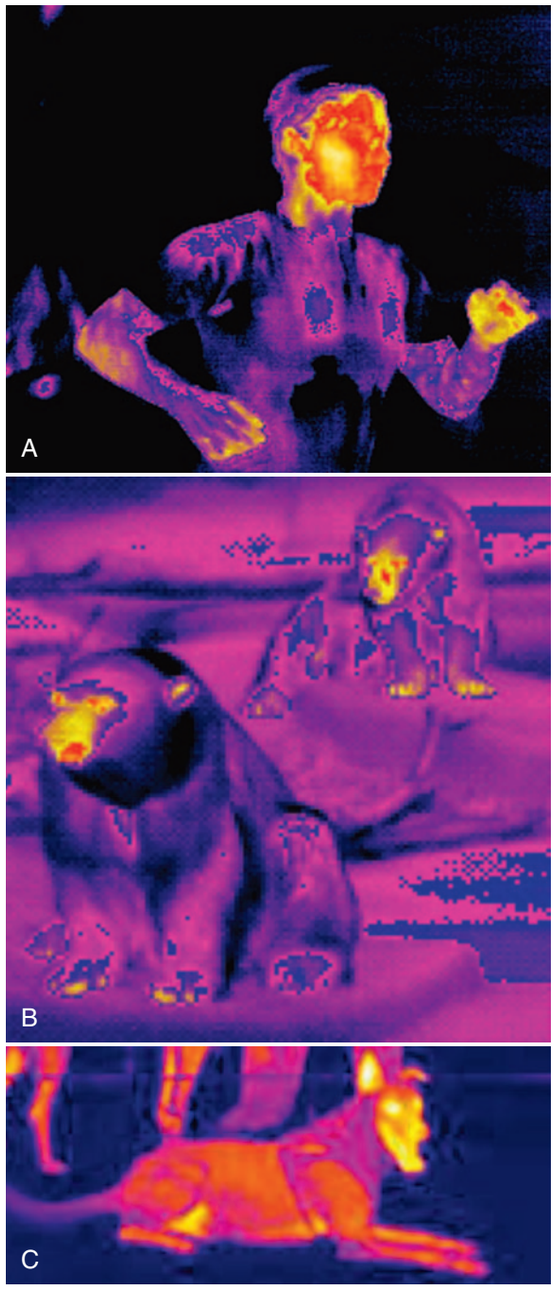

FIGURE 10-4 Infrared images of various surface regions. The brighter the color, the warmer the surface temperature. **A,** Female runner after 45 minutes of exercise in a 23° C (73.4° F) environment. Note that the palms of the hand and the face are substantially warmer than the rest of the body surface. **B,** Two polar bears. Note that only the snout, eyes, ears, and footpads are noticeably different from the surroundings. **C,** Sled dog relaxing shortly after completing the 17.7-km (11-mile) ceremonial starting leg of the 2005 Iditarod Trail Sled Dog Race. The course of the Iditarod is greater than 1850.7 km (1150 miles) from Anchorage to Nome, Alaska. Ambient conditions were 0° C (32° F)with a light overcast and no wind. The infrared shot shows that the dog's entire snout is white, meaning it is the hottest part of the body surface. The armpits and ears also are warmer. Maybe that is why dogs love to roll around in the snow, face first, on a warm day. *(**A** and **B** from Grahn D, Heller HC: The physiology of mammalian temperature homeostasis.* TraumaCare *14:52, 2004, with permission. **C** courtesy D. Grahn; photo by Matthew Grahn.)*

TABLE 10-1 Heat Illness Symptoms and Management

Condition	Symptoms	Management
Heat cramps	Brief, painful skeletal muscle spasms	Rest; replacement of electrolytes; avoid salt tablets
Heat rash (miliaria rubra)	Blocked eccrine sweat glands	Cool, dry affected skin area; topical corticosteroids, aspirin
Heat exhaustion	Mild to moderate illness with inability to sustain cardiac output; moderate (>38.5° C [101.3° F]) to high (>40° C [104° F]) body temperature; often accompanied by dehydration	Move supine individual to cool, shaded environment, and elevate legs; loosen or remove clothing, and actively cool skin; administer oral fluids
Heatstroke	Profound CNS abnormalities (agitation, delirium, stupor, coma) with severe hyperthermia (>40° C [104° F])	Ensure an open airway, and move to a cool environment. Immediately cool to <39° C (102.2° F) using ice packs, water bath, wetting with water and continuous fanning; IV fluid administration; reestablish normal CNS function; avoid antipyretics or drugs with liver toxicity

CNS, Central nervous system; *IV,* intravenous.

Data from Bouchama A, Knochel JP: Heat stroke. *N Engl J Med* 346:1978, 2002; and Winkenwerder W, Sawka MN: Disorders due to heat and cold. In Goldman L, Ausiello DA, Arend W, et al, editors: *Cecil textbook of medicine,* ed 23, Philadelphia, 2007, Saunders, pp 763-767.

F]) elevations in core temperature and an inability to sustain cardiac output.[335] The signs and symptoms of heat exhaustion include fatigue, dizziness, headache, nausea, vomiting, malaise, hypotension, and tachycardia with potential for collapse. Heat exhaustion can occur with or without exercise in hot environments and may progress to a moderately severe condition without associated organ damage. Heat exhaustion is often observed in older adults as a result of medications (e.g., diuretics), inadequate water intake that leads to dehydration, or preexisting cardiovascular insufficiency that predisposes to collapse. Treatment should consist of placing the individual in a recumbent position in a cool environment to normalize blood pressure. Oral fluid ingestion with electrolytes is often adequate for recovery; intravenous (IV) fluid administration may be warranted in severely dehydrated individuals.

Heat injury is a moderate to severe condition characterized by tissue (e.g., skeletal muscle) or organ (e.g., gut, kidney, spleen, liver) damage and hyperthermia (core temperature usually, but not always >40° C [104° F]).[335] Heat injury may progress to heatstroke if the patient is not rapidly cooled. Heatstroke is life threatening, with the patient presenting with profound CNS abnormalities, such as delirium, agitation, stupor, seizures, or coma and severe hyperthermia (core temperature typically, but not always >40° C [104° F]).[335] Reliance on a specific core temperature value for clinical diagnosis of heatstroke is ill advised, because there is wide interindividual variability in documented cases. One of the main reasons for a lack of clinical treatments for heatstroke is the complicated nature of the syndrome, because there are different classifications based on etiology and pathophysiologic mechanisms of injury. Classic (also known as passive) heatstroke occurs at rest in vulnerable individuals, such as infants and older adults. Several intrinsic factors may predispose infants to heatstroke death. These include increased surface area–to–body mass ratio (accelerates heat gain), limited effective mechanisms of thermoregulation (e.g., suppressed behavioral adjustments), increased risk for dehydration (e.g., lack of water availability), and preexisting respiratory infections. Many older individuals have preexisting conditions, such as mental illness, prescription drug use (e.g., diuretics, anticholinergics), or infections that predispose to passive heatstroke (Table 10-2).[6,56,312]

Exertional heatstroke (EHS) has a different etiology than does classic heatstroke and affects young healthy populations that perform strenuous physical activity or work in temperate or hot weather. During exercise, approximately 80% of expended energy is released as heat that must be dissipated from the body to avoid hyperthermia. Military and athletic populations are composed of young, healthy individuals who are highly motivated to perform strenuous physical activity in hot weather, which increases the risk for EHS. A recent epidemiologic study identified a variety of factors that predispose to EHS, including gender (women greater than men), geographic region of origin (northern greater than southern states), preexisting illness, and race or ethnicity (white greater than black).[40] Unfortunately, exercise induces physiologic responses similar to those of heat stress, such that teasing apart the influence of these two factors in EHS is difficult.

Heatstroke Epidemiology and Risk Factors

The ability to perform strenuous work in a hot environment is inversely related to the heat stress level, which can be assessed using the wet bulb globe temperature (WBGT) index. The WBGT for indoor or outdoor environments is determined in the following manner:

$$\text{Indoor WBGT} = 0.7\ T_w + 0.3\ T_{amb}$$

$$\text{Outdoor WBGT} = 0.7\ T_w + 0.2\ T_{bg} + 0.1\ T_{amb}$$

TABLE 10-2 Predisposing Risk Factors for Serious Heat Illness

Environmental Factors
High ambient temperature
High humidity
Lack of air movement
Trees and shrubbery
Access to air condition
Lack of shelter
Heat wave (3 or more days of temperatures >32.2° C (90° F))
Individual Factors
Age (small children, older adults)
Obesity
Poor physical fitness level
Lack of acclimatization
Dehydration
Drug Use
Diuretics
Anticholinergics (e.g., atropine)
β-blockers (e.g., propranolol)
Antihistamines
Amphetamines (e.g., Ecstasy)
Ergogenic aids (e.g., ephedra)
Antidepressants
Alcohol consumption
Compromised Health Status
Viral infection (e.g., pneumonia, mononucleosis)
Inflammation (e.g., fever)
Skin disorders (e.g., miliaria rubra, burns)
Cardiovascular disease
Diabetes mellitus
Malignant hyperthermia
Sickle cell trait

Data from references 6, 58, 196, 318, and 340.

where T_w is the natural wet bulb temperature, T_{bg} is the black globe temperature, and T_{amb} is the dry bulb temperature. T_{bg} determines the radiant heat load with a specialized thermometer that is surrounded by a 6-inch–diameter blackened sphere. The WBGT is the most widely used index to determine safe limits of physical activity and establish strategies to minimize the incidence of heat illness during military, athletic, or occupational tasks. The WBGT index does not take into consideration different clothing ensembles or exercise intensities, so the most practical and safe application of this measurement requires adjustment for these factors.

Heat waves are defined as three or more consecutive days during which the environmental temperature exceeds 32.2° C (90° F)[41] In the summer of 2003, Europe experienced 22,000 to 45,000 heat-related deaths during a 2 week period in which the average temperature was 3.5° C (6.3° F)above normal.[189,273] The European continent has experienced an increase in minimum daily temperatures over the last 30 years, and this trend will likely increase if average global temperatures continue to rise. A 1.4° to 5.8° C (2.5° to 10.4° F) increase in minimum daily temperatures in Europe is predicted over the next century.[131,337] Most prediction models suggest that heat waves in the future will be more severe and longer in duration. Predictions based on climate variability data from the 1995 Chicago and 2003 Europe heat waves suggest that by 2090, heat waves in these cities will be 25% to 31% more frequent and last 3 to 4 days longer.[203] Another prediction model suggests a 253% increase in annual heatstroke deaths in the United Kingdom by 2050.[61]

The impact of climate change is not equally distributed across the globe because of regional variability in thermal tolerance that influences the incidence of heatstroke mortality. A study of 11 U.S. cities showed that threshold temperatures for heatstroke mortality are higher in warmer southern cities than in cooler northern cities.[53] A comparison of temperature–mortality relationships in southern Finland, southeastern New England, and North Carolina indicated that lower temperature thresholds in cooler climates are coupled with steeper temperature–mortality relationships.[62] Similarly, the upper safety limit of environmental temperature in the Netherlands, London, and Taiwan is 16.5°, 19°, and 29° C (61.7°, 66.2°, 84.2° F), respectively.[192] A case study of 15 Marine recruits who collapsed from heatstroke during training exercises in South Carolina showed that 73% previously resided in northern states and that 60% of cases occurred during the second week of training during the hottest summer months.[232] From 1980 to 2002, the highest EHS incidence in military recruits was in nonacclimatized individuals from northern, cold-climate states who were enlisted for less than 12 months.[40] During July, many regions of the world have a WBGT index that is greater than 29° C (84.2° F), and military training often occurs in environments with a WBGT index that is greater than 35° C (95° F). During peacetime exercises, approximately 25% of fatal military EHS cases occur during the hottest summer months in recruits who have been in training camp less than approximately 2 weeks.[192] Individuals from northern states are expected to be less acclimatized to hot, humid summer conditions than are those from southern states. Heat acclimatization improves thermotolerance but requires several days to weeks of exposure to similar heat stress and exercise conditions to be fully effective. This likely accounts for hot days early in the summer showing a greater impact on heatstroke morbidity and mortality than those cases occurring later in the training process, after the protective effects of heat acclimatization have been realized.[105]

Humanity's impact on the landscape in conjunction with increased production of greenhouse gases may be creating the largest climate change. Urban heat islands are created in cities when vegetation is removed and blacktop roads and concrete buildings are erected. Temperatures may be 30° to 40° C (54° to 72° F) higher on asphalt roads and roof tops compared with those of the surrounding air.[85] Since 1978 urban sprawl has accounted for an increase in city temperatures in southeastern Asia of approximately 0.05° C (0.09° F) per decade.[343] Across the entire land mass of the United States, the surface temperature has increased approximately 0.27° C (0.49° F) per century because of changes in the land cover arising from agricultural and urban development.[139] Concrete and asphalt surfaces cool slowly during the nighttime when air temperature decreases, and this increase in urban heat storage magnifies the intensity of heat exposure experienced by individuals living in concrete urban structures.[49,165]

Several social factors predispose older adults to heatstroke mortality, including living alone, inability or unwillingness to leave one's home, residing on the top floor of buildings (heat rises), and annual income of less than $10,000.[221] Most heat wave early warning systems emphasize the use of air-conditioning systems, but availability and *use* of these units is limited by socioeconomic status because these units are expensive to operate.[56,221] A working air conditioner was the strongest protective factor against mortality during the 1999 heat wave in Chicago; fan cooling did not afford protection.[221] High mortality rates were recorded in Chicago despite extensive programs to educate high-risk populations, such as advising older adults to seek cool shelters or use air-conditioning systems. Approximately 10,000 elders died during the France heat wave of 2003 primarily because of lack of air-conditioning units in residences and hospitals.[63,312] In 2005, Hurricane Katrina ravaged the U.S. Gulf Coast, and electrical failures caused high heatstroke mortality of older adults confined to residences, retirement homes, and hospitals because local temperatures exceeded 43° C (109.4° F). Increases in the average human lifespan, global climate change, and use of medications that compromise cardiovascular adjustments to heat stress will necessitate increased reliance on artificial cooling systems and educational programs to prevent heatstroke deaths in vulnerable populations, such as older adults.

The high death toll of older adults because of excessive heat per se may be small compared with that caused by aggravation of a preexisting illness. *Heat stress* refers to environmental and metabolic conditions that increase body temperature; *heat strain* refers to the physiologic consequences of heat stress. Heat strain imposes large cardiovascular demands on the body. Blood flow is shunted from the viscera to the skin surface to dissipate excess heat to the environment, making cardiovascular fitness a more important factor than age in determining an individual's susceptibility to heatstroke. Austin and Berry[10] examined 100 cases of heatstroke during three summer heat waves in St. Louis and found cardiovascular illness in 84% of patients. Levine[178] found heatstroke deaths to be associated with arteriosclerotic heart disease (72%) and hypertension (12%). Cardiac deficiency impedes heat loss and compromises the ability to maintain cardiac output during prolonged heat exposure, leading to circulatory collapse and death. Older individuals may have impaired baroreceptor reflex modulation, lower sweat rates, longer time to onset of sweating, and diminished sympathetic nerve discharge, all of which increase the risk for heatstroke morbidity and mortality.[130,144,291] Minson and colleagues[206] demonstrated that during heat exposure, older men relied on a higher percentage of their cardiac chronotropic reserve compared with young men.

Preexisting infection or inflammation may compromise an individual's ability to appropriately respond to heat stress and can be a complicating factor, regardless of age. Fifty-seven percent of heatstroke patients more than 65 years old had evidence of infection upon clinical admission during a Chicago heat wave in 1995.[56,157] In Singapore, a young EHS victim had been ill for 3 days before heatstroke collapse.[43] It has been proposed that acute illness or inflammation can cause transient susceptibility to heatstroke in young, fit individuals who exercise in the heat. For example, idiosyncratic episodes of hyperthermia were associated with acute cellulitis and gastroenteritis in soldiers exercising in the heat.[39,146] Four male Marine recruits presented with viral illness (mononucleosis, pneumonia) before collapse from exertional heat illness (EHI) during training exercises associated with "the Crucible" at Parris Island, South Carolina.[289] Peripheral blood mononuclear cells (PBMCs) from these recruits expressed higher levels of IFN-inducible genes than did those from controls who participated in the training event but did not collapse.[289] High plasma levels of IFN-α and IFN–γ mediate flulike symptoms during viral infection and are often associated with EHI/EHS.[24,289] In rats, exposure to lipopolysaccharide (LPS), a cell wall component of gram-negative bacteria, exacerbated inflammation, coagulation, and multiorgan system dysfunction from heat exposure.[182] Taken together, these findings suggest that a

preexisting inflammatory state compromises an individual's ability to respond to heat stress with appropriate thermoregulatory or immune responses to prevent collapse or multiorgan system failure and death.

The annual Muslim pilgrimage to Mecca (the hajj) is associated with high heatstroke incidence each year and provides many lessons regarding etiologic factors that increase susceptibility. The hajj takes place in the hot desert environment of Saudi Arabia during the extreme weather months of May to September, when temperatures range from 38° to 50° C (100.4° to 122° F).[148] Hot weather combined with physical exertion (first day consists of a 3.5-km [2.2-mile] jog), heavy clothing that is traditional to the region (limits heat dissipation), and an older population (approximately 50 years is an advanced age for this region) predispose many individuals to heatstroke. Clothing has a significant impact on Muslim women because they are required to wear darker clothing that covers a larger surface area of the body than does clothing worn by men.[112] Medical conditions, such as diabetes, cardiovascular abnormalities, or parasitic diseases, are common.[148] Heatstroke is a major concern, but heat exhaustion with water or salt depletion is also prevalent. Overcrowding and congestion impose large demands on sanitation services, as exemplified in the 1980s, when approximately 2 million people participated in the hajj. Advances in modern technologies, such as more rapid transport to the area, will likely introduce additional factors (e.g., lack of acclimatization, increased greenhouse gas production, increased congestion) to this already complex situation.

Protective clothing is a significant predisposing factor to EHS during athletic (heavy uniforms), military (chemical protective clothing), or occupational activities (e.g., pesticide application, firefighting, and race car driving). Protective clothing often consists of multiple layers that insulate anatomic sites from heat exchange, including the skin and head.[251] The wearing of protective clothing during strenuous work can quickly result in a dangerous elevation in body temperature. Fifty-one cases of EHI were observed in military trainees in San Antonio, Texas, during participation in a 9.3-km (5.8-mile) march in full battle dress uniform and boots.[285] Lack of acclimatization to athletic uniforms and high environmental temperatures results in the majority of EHS occurring on the second or third day of exposure to hot weather before these individuals are acclimatized to the uniforms and environmental temperatures.[97,260]

SKIN DISORDERS

The skin is the largest organ of the body and an important area for effective heat exchange with the environment. There are a number of skin disorders that can adversely affect temperature control and increase susceptibility to heat illness. Miliaria rubra (also known as prickly heat, sweat rash, or heat rash) occurs when sweat gland ducts become blocked with dead skin cells or bacteria (e.g., *Staphylococcus epidermidis*). The obstruction causes eccrine secretions of the sweat glands to accumulate in the ducts or leak into the deeper layers of the epidermis, causing a local inflammatory reaction associated with redness and blister-like lesions. Individuals with miliaria rubra are at increased risk for heat illness when a large area of the skin is affected. If heat illness is expected, the affected area of the skin should be cooled and dried to control infection, and topical corticosteroids or aspirin may be effective in reducing swelling and irritation. Sunburn can impair sweating and cause fever, which increase the risk for heat illness. If the sunburn covers more than 5% of the body, heat exposure should be avoided until the skin has healed. Sunburn is a preventable disorder with the use of sun-block lotions, protective clothing, and shelter from sun exposure.

Pathophysiology of Heatstroke

The pathophysiologic responses to heatstroke range from those conditions that are experienced immediately following collapse to long-term changes that persist for several weeks, months, or years following hospital treatment and release. Currently more is known about the immediate heatstroke because clinical records document symptoms during hospital treatment. However, clinical and experimental research has seen a shift within the past decade toward a focus on understanding the pathophysiologic responses that mediate long-term injury. It is now believed that the long-term pathophysiologic responses to heatstroke are caused by a systemic inflammatory response syndrome (SIRS) that ensues following heat-induced damage to the gut and other organs.[24] Following damage to the epithelial membrane of the gut, endotoxin that is normally confined to the lumen of this organ is able to leak into the systemic circulation and elicit immune responses that cause tissue injury. The thermoregulatory, immune, coagulation, and tissue injury responses that ensue during long-term progression of heatstroke closely resemble those observed during clinical sepsis and are likely mediated by similar cellular mechanisms. Clinical records have provided an extensive database of the immediate consequences of heatstroke, whereas the majority of knowledge regarding the pathophysiologic mechanisms of heat-induced SIRS has been obtained from experimental animal studies. Although there are several gaps in our knowledge of the specific factors that predispose to multiorgan system failure, this is an exciting area of research that is expected to progress at a rapid rate because of continued advancements in experimental and genetic technologies. Figure 10-6 provides an overview of the current understanding of the pathophysiologic responses that are thought to initiate and mediate heat-induced SIRS, which will be discussed in detail here.

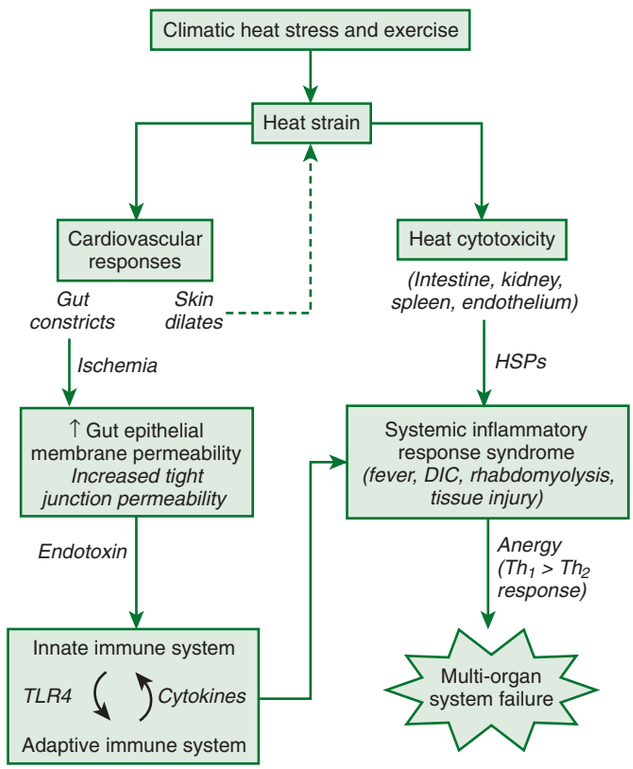

FIGURE 10-6 Summary of heatstroke pathophysiologic responses that culminate in multiorgan system failure. An increase in heat strain stimulates a reflexive increase in cutaneous blood flow and decrease in splanchnic blood flow to facilitate heat dissipation to the environment. Gut ischemia causes increased epithelial membrane permeability and leakage of endotoxin into the systemic and portal circulation. Toll-like receptors (e.g., TLR4) detect pattern-associated molecular patterns on the cell membrane of endotoxin and stimulate proinflammatory and antiinflammatory cytokine production. Heat is toxic to several organs and stimulates the secretion of heat shock proteins (*HSPs*) that interact with cytokines and other proteins to mediate the systemic inflammatory response syndrome (SIRS) of the host. Peripheral and central nervous system actions of cytokines and other mediators of SIRS are thought to mediate many of the adverse consequences of the heatstroke syndrome that lead to multiorgan system failure and death. *DIC,* Disseminated intravascular coagulation.

TABLE 10-3 Clinical Characteristics of Exertional Heat Illness Cases

Activity	Body Temperature (° C [° F])	Age (Years)	Length of Hospitalization	Outcome
Military training				
Army (aviation)	>39.0 (102.2)	18-59	10 min	CNS dysfunction[207,*]
Army (basic)	40-41.1 (104-106)	18-41	24 hr to 12 days	Death[192]
Army (basic)	41.1 (106)	20	5 days	Recovery[233]
Army (Singapore)	40-42 (104-107.6)[†]	18-29	45 min to 99 hr	Death[43]
Marine Corps	<38.9-40.0 (102-104)	17-30	None	Recovery[106]
Marine Corps	39-42.5 (102.2-108.5)[†‡]	17-19	>1 day	Recovery[289]
Marine Corps	41.1 (106)	NR	≤12 hr	Hospitalization[106]
NBC	41.3 (106.3)	25	12 days	Recovery[51]
Athletic events				
6-Mile run	39.2 (102.6)[§]	29	10 days	Death[204]
Marathon run	40.7 (105.3)[‡]	Late 30s	5 days	Recovery[261]
Marathon run	41.9 (107.4)	26	None	Recovery[197]
Hajj rituals	<42 (107.6)	32-80	NR	Ataxia, infarction, death[341]
	≥42 (107.6)	NR	NR	Death[341]
	43.9 (111)	NR	NR	Recovery[341]
Migrant farming	42.2 (108)	44	None	Death[220]
Firefighter training	42.6 (108.7)	22	9 days	Death[219]

NR, Not reported; *NIOSH*, National Institute for Occupational Safety and Health; *NBC*, nuclear, biological, and chemical protective clothing.
*CNS dysfunction includes agitation, confusion, disorientation, delirium, poor memory, convulsions, and/or coma.
†Indicates patient cohorts with documented prodromal illness before heatstroke collapse.
‡Body temperature measured several minutes after collapse or cooling.
§Patient temperature increased to 41° C (105.8° F) on day 10 of hospitalization before death.

BODY TEMPERATURE RESPONSES

At the time of heatstroke collapse, the severity of hyperthermia varies widely between individuals, with reported core temperature values ranging from approximately 41° C (105.8° F) to approximately 47° C (116.6° F).* During a summer heat wave in St. Louis in the 1950s, core temperature of 100 heatstroke patients ranged from 38.5° to 44° C (101.3° to 111.2° F), with 10% of mortalities occurring below 41.1° C (106° F).[10] In some instances, individuals may tolerate hyperthermia without adverse side effects. During a competitive marathon race in California, a 26-year-old man maintained a rectal temperature of 41.9° C (107.4° F) for approximately 45 minutes without clinical signs of heat illness.[197] However, there are several reports of athletic, military, and occupational workers with core temperatures below 41.9° C (107.4° F) that were hospitalized, experienced permanent CNS impairment, or died from EHS (Table 10-3).

Hypothermia and fever are core temperature responses that are often observed in patients and experimental animal models during heatstroke recovery. Hypothermia is not a universal heatstroke recovery response in humans but has been anecdotally observed following aggressive cooling treatment. Hypothermia manifests as a rapid undershoot of body temperature below 37° C (98.6° F) and is thought to represent a loss of thermoregulatory control following heat-induced damage to the POAH. However, evidence in support of this hypothesis is lacking because autopsy reports and experimental animal studies have failed to detect histologic damage to the POAH despite extensive damage in other organs.[174,192] Because hypothermia is not observed in all heatstroke patients, it continues to be regarded as a pathologic recovery response. In experimental animals, hypothermia is a natural heatstroke recovery response that is associated with behavioral and autonomic thermoeffector responses that support a decrease in core temperature. Mud puppies are ectothermic species that rely on behavioral adjustments, such as the selection of different microclimates, to control body temperature. Mud puppies heat shocked to approximately 34° C (93.2° F) behaviorally selected a cooler microclimate and maintained a significantly lower body temperature than did nonheated controls during 3 days of recovery.[128] This study did not determine the impact of hypothermia on survival, but the association of decreased body temperature with the selection of cool microclimates indicated that this was a regulated response to a decrease in the temperature set point. Small rodents, such as mice, rats, and guinea pigs, showed reductions greater than 1.0° C (1.8° F) in body temperature that were associated with improved survival following passive heatstroke. In mice, hypothermia was associated with an approximately 35% decrease in metabolic heat production and the behavioral selection of microclimates that precisely regulated the depth and duration of this response.[174] Exposure of mice to warm ambient temperatures that prevented heat-induced hypothermia caused increased intestinal damage and mortality.[173,333] Hypothermia likely provides protection against heat-induced tissue injury in a manner similar to that shown for protection against other extreme environmental insults based on the temperature coefficient (Q_{10}) effect.

A common heatstroke recovery response observed in patients and animal models is recurrent fever during the days and weeks of recovery.[9,10,173,192,204] In mice, fever was observed within a day after passive heatstroke collapse and associated with an approximately 20% increase in metabolic heat production and increased plasma levels of the proinflammatory cytokine interleukin (IL)-6.[154,172,174] IL-6 is an important regulator of fever during infection and inflammation and may regulate fever during heatstroke recovery.[172] In patients, fever is reestablished following clinical cooling.[192] This is reminiscent of Liebermeister's experimental observations of the recurrence of fever following experimental cooling of the POAH of rats.[180,192] In experimental animal models, the inability to recover from hypothermia and develop fever is associated with increased mortality, suggesting that fever may be important for the resolution of infection.[173] However, in a case report of human heatstroke, fever was associated with poor outcome. An amateur long-distance runner was hospitalized for 10 days after collapsing from EHS during a 9.7-km (6-mile) footrace.[204] Moderate fever (>38° C [100.4° F]) was evident during the first 4 days of hospitalization, but on the 10th day the patient experienced convulsions and a rapid increase of body temperature to 41° C (105.8° F). Rapid cooling and aspirin were ineffective in reducing body temperature, and the patient died.[204] The inability of aspirin to inhibit the rapid rise in body temperature suggests that this was not a true fever response, but rather a pathologic response to increased metabolic heat production induced by the convulsions. It is important to recognize that there is an optimal temperature range above which the protective effects of fever are no longer realized because of the toxic effect of high body temperature on cell function.[155]

IMMUNE RESPONSES

During heat stress, blood flow to the skin is increased to facilitate heat loss to the environment and reduce the rate of total body

*References 26, 42, 109, 112, 188, 289.

heat storage. Increased skin blood flow is accompanied by a fall in splanchnic (i.e., visceral organ) blood flow as a compensatory mechanism to sustain blood pressure. Endotoxin is normally confined to the gut lumen by tight junctions of the epithelial membrane, but these junctions can become "leaky" following prolonged reductions in blood flow that cause ischemic stress.[108,164] There are several lines of evidence that support the hypothesis that endotoxin leakage from the gut lumen into the systemic circulation is the initiating stimulus for heat-induced SIRS. First, systemic injection of LPS into experimental animals induces symptoms similar to those observed in heatstroke, including hyperthermia, hypothermia, fever, hypotension, cytokine production, coagulation, and tissue injury.[175,268] Second, increased portal or systemic endotoxin levels are observed in heatstroke patients and animal models. In primates, circulating endotoxin was detected at rectal temperatures above 41.5° C (106.7° F) with a precipitous increase at approximately 43.0° C (109.4° F).[90] Splanchnic blood flow shows an initial decrease at 40° C (104° F); the liver, which is an important clearance organ for endotoxin, shows damage at body temperatures of approximately 42° to 43° C (107.6° to 109.4° F).* In a young athlete with a body temperature of 40.6° C (105.1° F) on the second day of football practice, high circulating levels of endotoxin were associated with hemorrhagic necrosis of the liver.[97] In heatstroke patients, endotoxin was detected at approximately 42.1° C (107.8° F) and remained elevated despite cooling.[26] Third, rats rendered endotoxin tolerant following the systemic injection of LPS are protected from heatstroke mortality.[66,67] The protective effect of endotoxin tolerance is related to enhanced stimulation of the liver reticuloendothelial system (RES), which is composed of monocytes, macrophages, and Kupffer cells that are important for endotoxin clearance.[66,67] In rats, RES stimulation reduced and RES blockade increased mortality of heat-stressed rats.[67] Fourth, antibiotic therapy protects against heatstroke in several species. In dogs, antibiotics reduced gut flora levels and improved 18-hour survival rates by more than threefold when provided before heat exposure.[37] In rabbits with heatstroke, hyperthermia and endotoxemia were reduced following oral antibiotics.[36] Anti-LPS hyperimmune serum reversed heatstroke mortality of primates and returned plasma LPS levels to baseline, but it was ineffective at the highest body temperature of 43.8° C (110.8° F), indicating that hyperthermia can cause irreversible organ damage and death.[91]

Heat-induced SIRS is initiated by the innate and adaptive immune systems, which interact to sense the presence of endotoxin and orchestrate an immunologic response. The innate immune system comprises monocytes, macrophages, and neutrophils that use pattern recognition receptors (PRRs) on their cell surfaces to recognize pattern-associated molecular patterns (PAMPs) on the cell surface of endotoxin and other invading pathogens.[137] Toll-like receptors (TLRs) are a class of PRRs that have been widely studied in the immune response to infection.[208,314] Ten mammalian TLRs have been identified, and the specific pathogenic ligands that activate these PRRs are known (Table 10-4).

TLR4 is the principal receptor for LPS that stimulates gene transcription factors, such as NF-κB to increase the synthesis of a variety of immune modulators in response to endotoxin. Endotoxin infection (i.e., sepsis) is associated with increased expression of TLR4 on circulating human PBMCs, as well as on mouse liver and spleen macrophages.[307,308] In the 1960s, a spontaneous mutation in the TLR4 gene was discovered in C3H/HeJ mice, which has been an important animal model to determine the role of TLR4 in endotoxin responsiveness. C3H/HeJ mice show a diminished response to bacterial infection, but increased mortality from SIRS, because of an inability to respond appropriately to endotoxin and induce the full complement of immune responses.[103] An inability to respond to antigens is known as anergy and is a proposed mechanism that predisposes to increased risk and mortality from bacterial infection.[117] Given that TLR4 mutations exist in humans, this may be one (of several) genetic factors that predispose to mortality associated with heat-induced SIRS, although the association of mortality with TLR4 polymorphisms remains controversial.[5,75] C3H/HeJ mice have not been tested for their resistance to heatstroke morbidity/mortality but are a useful experimental model to determine the role of TLR4 and anergy in this syndrome.

Specificity of immune responses is provided by B and T cells of the adaptive immune system. These cells respond to antigens by secreting cytokines, which are intercellular immune signals that elicit proinflammatory (Th1 type) and antiinflammatory (Th2 type) actions during progression of SIRS. The actions of cytokines depend on the nature of the danger signal, the target cells with which they interact, and the cytokine "milieu" in which they function. Th1 and Th2 cytokines function in a negative feedback pathway to regulate each other's production and maintain a delicate balance of inflammatory reactions. Anergy is thought to be a consequence of inadequate Th2 cytokine production late in SIRS. For example, increased patient mortality from peritonitis is associated with the inability to mount a Th2 cytokine response.[117]

Alarmins are endogenous PAMPs that are released from stressed or injured tissues and initiate restoration of homeostasis following an infectious or inflammatory insult.[17] High mobility group box 1 (HMGB1) is a highly conserved nuclear protein that functions as an alarmin following release from necrotic (but not apoptotic) cells.[272] Necrosis is the premature death of cells in a tissue or organ in response to external factors, such as pathogens and toxins. Because necrosis is detrimental to the host, it is

TABLE 10-4 Toll-Like Receptors of the Innate Immune System

Toll-Like Receptor	Ligand	Cell/Tissue Types
TLR1	Triacyl lipopeptide	Monocytes, macrophages, DCs, polymorphonuclear leukocytes, B and T cells, NK cells
TLR2	Lipopolysaccharide Peptidoglycan Lipoteichoic acid Measles virus Human cytomegalovirus Hepatitis C virus Zymosan Necrotic cells	Monocytes, granulocytes Brain, heart, lung, spleen
TLR3	Viral double-stranded RNA	DCs, T cells, NK cells, monocytes, granulocytes Placenta, pancreas
TLR4	Lipopolysaccharide Fibrinogen Heat shock proteins High mobility group box 1	B cells, DCs, monocytes, macrophages, granulocytes, T cells Spleen
TLR5	Flagellated bacteria	Monocytes Ovary, prostate
TLR6	Diacyl lipopeptide	B cells, monocytes Thymus, spleen, lung
TLR7	Single-stranded RNA	Monocytes, B cells, DCs Lung, placenta, spleen, lymph node, tonsil
TLR8	Single-stranded RNA	Monocytes Lung, placenta, spleen, lymph node, bone marrow, PBLs
TLR9	CpG DNA	B cells, DCs Spleen, lymph node, bone marrow, PBLs
TLR10	Unknown	B cells Spleen, lymph node, thymus, tonsil

CpG, Deoxycytidylate-phosphate-deoxyguanylate; *DC,* dendritic cell; *NK,* natural killer; *PBL,* peripheral blood leukocyte..

Data from Medvedev AE, Sabroe I, Hasday JD, et al: Tolerance to microbial TLR ligands: Molecular mechanisms and relevance to disease. *J Endotoxin Res* 12:133, 2006; and Tsujimoto H, Ono S, Efron PA, et al: Role of Toll-like receptors in the development of sepsis. *Shock* 29:315, 2008.

*References 29, 30, 43, 108, 147, 225.

associated with an inflammatory response. Apoptosis refers to genetically programmed cell death that does not elicit an inflammatory response, because apoptosis is beneficial to the host. The release of HMGB1 from necrotic cells stimulates Th1 cytokine production late in the sepsis syndrome and is a purported mediator of lethality; this shift in the balance of cytokines from a Th2 to Th1 phenotype is a potential mechanism of sepsis lethality. In human PBMCs, HMGB1 interacts with TLR2 and TLR4 to enhance Th1 cytokine production in synergy with LPS.[124] Elevated serum HMGB1 levels are observed 8 to32 hours following LPS injection in mice. Anti-HMGB1 antibodies did not protect against LPS-induced mortality unless the antibodies were provided 12 and 36 hours after LPS exposure.[324] The delayed kinetics of HMGB1 and the association of elevated serum levels of this protein with poor outcome in sepsis patients suggest that HMGB1 detection late in SIRS may be a sensitive clinical marker of disease severity.[115,297,324]

COAGULATION

Disseminated intravascular coagulation (DIC) is a common clinical symptom of heatstroke and manifests as two different forms (Figure 10-7).

Microvascular thrombosis is a form of DIC characterized by fibrin deposition and/or platelet aggregation that occludes arterioles and capillaries and predisposes to multiorgan system dysfunction.[177] Microvascular thrombosis is commonly observed in response to sepsis or trauma. DIC associated with consumptive coagulation is characterized by excessive blood loss when platelets and coagulation proteins are consumed faster than they are produced.[8,12] Hemorrhagic complications in heatstroke victims include prolonged bleeding from venipuncture sites or other areas (e.g., gums), which can have a fatal outcome.[148] The primary event that initiates coagulation in heatstroke patients is thermal injury to the vascular endothelium.[21,24,215] In vitro studies have shown the ability of heat (43°-44° C [109.4°-111.2° F]) to directly activate platelet aggregation and cause irreversible hyperaggregation despite cooling.[87,333] Cancer patients treated with whole-body hyperthermia (41.8° C [107.2° F]) for 2 hours) showed decreased fibrinogen and plasminogen at body temperatures as low as 39° C (102.2° F), alterations in factor VII activity at 41.8° C (107.2° F), and decreased platelet concentrations from the time of maximum body temperature through 18 hours of recovery.[295]

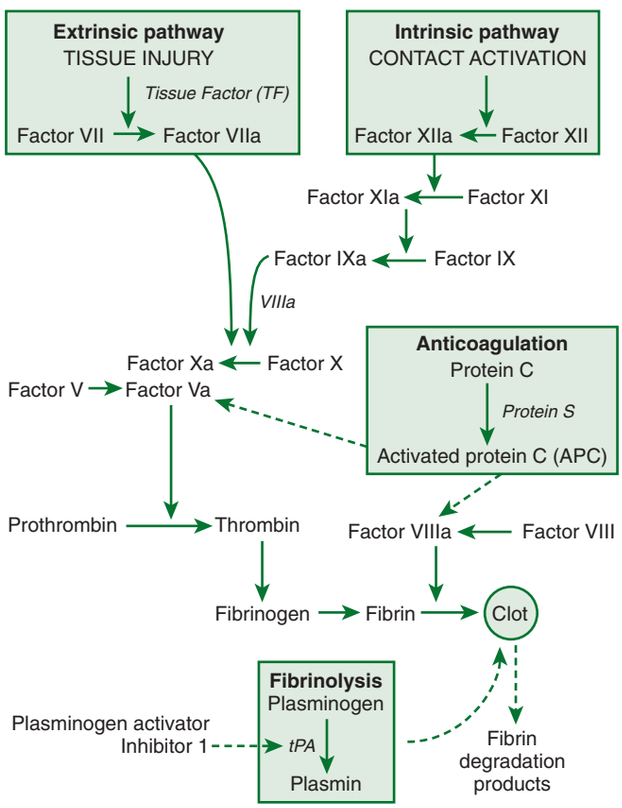

FIGURE 10-7 Pathways of disseminated intravascular coagulation (DIC). The coagulation cascade is stimulated by the extrinsic pathway (also known as the tissue factor [TF] pathway) and the intrinsic pathway (also known as the contact activation pathway). Both pathways represent a series of enzymatic reactions that result in formation of a fibrin clot. Fibrinolysis represents the pathway by which the fibrin clot is resorbed through the actions of plasmin. The major physiologic anticoagulant is protein C, which is activated by protein S and inactivates factors Va and VIIIA to inhibit clot formation. Lipopolysaccharide, interleukin-1, and tumor necrosis factor affect DIC by stimulating TF formation and inhibiting the inactivation of factors Va and VIIIa, which prolongs clot formation.

Several proteins, including HMGB1, IL-1, tumor necrosis factor (TNF), and activated protein C (APC), affect the coagulation, anticoagulation, and fibrinolytic pathways. In rats, HMGB1 in combination with thrombin caused excess fibrin deposition in glomeruli, prolonged clotting times, and increased sepsis mortality compared with thrombin alone.[133] The effect of HMGB1 protein was demonstrated in vitro to be caused by inhibition of the APC pathway and stimulation of tissue factor expression on monocytes.[133] Cytokines stimulate microvascular thrombosis by interacting with neutrophils, macrophages, platelets, and the endothelium to increase the expression of intracellular adhesion molecules. Increased expression of cell adhesion molecules, neutrophil adhesion, and release of reactive oxygen species caused endothelial activation and injury.[201,330] APC is an important component of the anticoagulation pathway that inactivates factors Va and VIIIa to inhibit fibrin clot formation. In septic patients, reduced APC production was associated with increased risk for mortality from systemic inflammation and DIC.[78,179] In addition to its anticoagulation properties, APC possessed antiinflammatory and antiapoptotic properties that protected against experimental sepsis and heatstroke.[44,302]

Typical clinical measures of coagulation include prothrombin time (PT), activated partial thromboplastin time (aPTT), and fibrinogen. PT in combination with aPTT assesses the time for plasma clot formation to occur in response to exogenous tissue factor and is a sensitive measure of responsiveness of the coagulation pathway. The reference range for PT is approximately 12 to 15 seconds and may be prolonged severalfold in heatstroke patients. The aPTT normally ranges from approximately 30 to 40 seconds and is used clinically to monitor treatment effects of anticoagulants, such as heparin. Fibrinogen is an acute phase protein synthesized by the liver that is normally in the range of 2 to 4 g/L. Low fibrinogen levels indicate liver damage or DIC, whereas elevated levels are a clinical sign of systemic inflammation. DIC can be difficult to diagnose, but low fibrinogen levels with prolonged PT or aPTT are strong clinical indicators in critically ill patients.

TISSUE INJURY

Multiorgan system failure is the ultimate cause of heatstroke mortality and is a consequence of SIRS, which ensues following heat-induced damage to the gut and other tissues.[24] A variety of noninfectious and infectious clinical conditions are associated with SIRS, and similar physiologic mechanisms are thought to mediate the pathogenesis of these conditions (Table 10-5).

The term *sepsis* refers to SIRS associated with the presence of infection. Much of the understanding of pathophysiologic mechanisms mediating heat-induced SIRS has been obtained from sepsis studies. Provided here is an overview of the responses that constitute heat-induced SIRS and current understanding of the pathophysiologic mechanisms that mediate the adverse events of this syndrome.

The severity of heatstroke is primarily related to the extent of damage to the brain, liver, and kidneys and is clinically identified by elevations in serum biomarkers, such as creatine kinase (CK), blood urea nitrogen (BUN), aspartate aminotransferase (AST), and alanine aminotransferase (ALT). CK is released from muscle and is a marker of skeletal muscle injury (also known as

TABLE 10-5 Common Factors in Heat Illness and Sepsis

Clinical
Neurologic symptoms (fatigue, weakness, confusion, stupor, coma, dizziness, delirium)
Tachycardia
Nausea, vomiting, diarrhea
Headache
Hypotension
Oliguria, multiorgan system failure
Hyperventilation
Shock
Laboratory
Metabolic acidosis
Elevated hematocrit
Elevated blood urea nitrogen (BUN), aspartate aminotransferase (AST) and alanine aminotransferase (ALT)
Elevated lactate
Disseminated intravascular coagulation
Elevated cytokines
Circulating endotoxin

rhabdomyolysis), myocardial infarction, muscular dystrophy, and acute renal failure.[1,274,322] BUN is a measure of the amount of nitrogen in the blood in the form of urea, which is secreted by the liver and removed from the blood by the kidneys. A high BUN concentration is typically regarded as an indication of impaired renal function, although BUN levels may be altered by conditions unrelated to heat illness, including malnutrition, high-protein diets, burns, fever, and pregnancy.[1,267] AST is released by the liver and skeletal muscle and may be a clinical sign of congestive heart failure, viral hepatitis, mononucleosis, or muscle injury. ALT is released by the liver, red blood cells, cardiac muscle, skeletal muscle, kidney, and brain tissue. AST and ALT are common clinical markers of liver function in heatstroke patients despite multiple tissue sources of these enzymes and occasional false-negative results that complicate interpretation. Unfortunately, all of these biomarkers are released by a variety of tissues and altered by heat-exhaustive exercise, so they do not always provide a precise measure of the extent of tissue injury.[95,102,283] The extent and time course of organ injury vary widely between individuals. Tissue injury manifests as primary and/or secondary multiorgan dysfunction, depending on whether heat toxicity alone or in combination with SIRS causes cellular damage.[4,192] Gut epithelial barrier disruption is an example of primary organ dysfunction that is evident at the time of heatstroke collapse. Hyperthermia degrades epithelial membrane integrity and causes microhemorrhages, dilation of the central lacteals of the microvilli, and blood clots within the stomach and small intestine (Figure 10-8).[27,108,172]

It is often difficult to determine if organ injury is caused by primary or secondary factors.* For example, protein clumping in kidney tubular epithelial cells may be a consequence of heat toxicity, elevated myoglobin levels, or DIC.† A conscious mouse model has shown that kidney damage is present within approximately 2 hours following heatstroke collapse and remains elevated through approximately 24 hours of recovery.[172] In heatstroke patients, acute renal failure is a nearly universal finding that is accompanied by decrements in function within 24 hours of admission to the intensive care unit.[244] In patients that survive more than 24 hours, severe hypotension, dehydration, BUN, and oliguria are associated with tubular necrosis or intertubular edema.[192] Primary changes in the spleen are even less well understood, but cytoplasmic protein clumping is thought to be a consequence of this organ being "simply cooked and coagulated."[43,172]

*References 21, 56, 97, 171, 172, 192.

†Reference 27, 43, 97, 147, 172, 188, 249, 323.

CNS dysfunction is a hallmark of heatstroke that is dominant early in the disorder. Patients are often confused, delirious, combatant, or comatose at the time of clinical presentation. Hyperthermia with exercise is also associated with reduced cerebral blood flow, which may account for these CNS abnormalities.[228] Despite rapid treatment, approximately 30% of heatstroke survivors experience permanent decrements in neurologic function.[6,24,56] CNS dysfunction is often associated with cerebral edema and microhemorrhages at autopsy in heatstroke patients.* The blood–brain barrier (BBB) is a semipermeable membrane that allows selective entry of substances (e.g., glucose) into the brain while blocking the entry of other substances (e.g., bacteria). Hyperthermia increases BBB permeability in experimental animal models, which permits leakage of proteins and pathogens from the systemic circulation into the brain. Computed tomography (CT) scans have been used to examine CNS changes in heatstroke patients. In the 1995 Chicago heat wave, atrophy, infarcts of the cerebellum, and edema were evident in older adult victims. CT scans also revealed severe loss of gray-white matter discrimination (GWMD), which was associated with headache, coma, the absence of normal reflexive responses, and multiorgan dysfunction.[299] The loss of GWMD is a consequence of increased brain water content, which is in line with the occurrence of edema in heatstroke victims. If GWMD provides an early, sensitive measure of brain injury, it will be a powerful prognostic indicator of outcome for heatstroke patients.

EHS is often associated with rhabdomyolysis, which is a form of skeletal muscle injury caused by the leakage of muscle cell contents into the circulation or extracellular fluid. Myoglobin released from damaged muscle cells is filtered and metabolized by the kidneys. When severe muscle damage occurs, the renal threshold for filtration of myoglobin is exceeded, and this protein appears in the urine in a reddish brown color.[86] Myoglobin is toxic to nephrons and causes overproduction of uric acid, which precipitates in the kidney tubules to cause acute renal failure, coagulopathy, and death if not rapidly detected and treated.[11,86,185,242,523] Not all cases of rhabdomyolysis are associated with myoglobinuria; many patients can be asymptomatic. Clinical

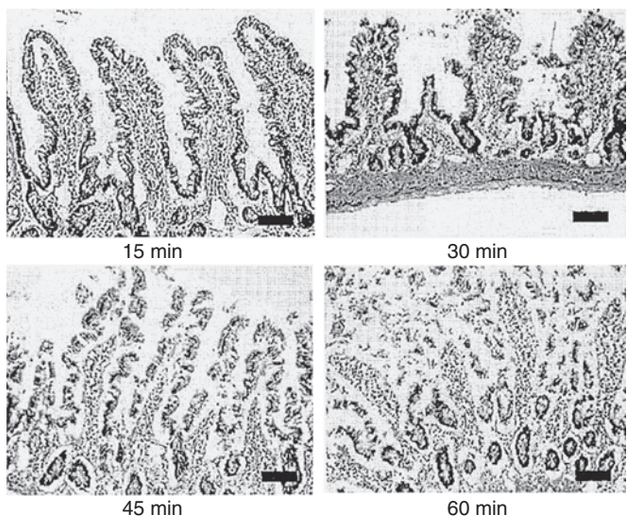

FIGURE 10-8 Effect of heating on villus structure. Representative light micrographs of rat small intestinal tissue over a 60-minute course at 41.5° to 42° C (106.7° to 107.6° F). Note the generally normal-appearing villi at 15 minutes (slight subepithelial space at villous tips), compared with initial sloughing of epithelia from villous tips at 30 minutes, massive lifting of epithelial lining at top and sides of villi at 45 minutes, and completely denuded villi at 60 minutes. Bars represent 100 µm. *(From Lambert GP, Gisolfi CV, Berg DJ, et al: Selected contribution: Hyperthermia-induced intestinal permeability and the role of oxidative and nitrosative stress,* J Appl Physiol *92:1750, 2002, with permission.)*

*References 48, 140, 192, 281, 282, 284, 299.

markers of rhabdomyolysis include elevated myoglobin, CK, aldolase, lactate dehydrogenase, ALT, and AST, which are influenced by a variety of factors (type, intensity, and duration of exercise; gender; temperature; altitude) and released by more than one organ or tissue.[50,205,263] If a clinical diagnosis of rhabdomyolysis is confirmed, immediate medical attention is imperative because approximately 50% mortality rates from acute renal failure have been documented for this condition.

Liver failure is one of the most common causes of morbidity and mortality in patients during the later stages of recovery. The time course of liver damage differs from that of the other organs and often does not peak until approximately 24 to 48 hours after heat exposure. For example, liver damage consisting of centrilobular degeneration and necrosis with parenchymal damage was only evident in EHS patients that survived more than 30 hours.[192] In addition, enhanced breakdown of fat or an inability of the mitochondria to use fat results in heatstroke-associated fatty liver changes.[43] Disturbances in plasma glucose homeostasis are a sign of liver damage that may cause hyperglycemia or hypoglycemia as a result of dysfunction of phosphoenolpyruvate carboxykinase, which is a regulatory enzyme of the liver's gluconeogenic pathway.[21,171,172] Liver dysfunction may also contribute to increased circulating endotoxin levels because of the important bacterial-clearance function of this organ.[30,225] Unfortunately, many heatstroke patients require liver transplantation. Use of antipyretic drugs, such as acetaminophen (Tylenol), has been associated with hepatic failure.[93,113,114,269,319]

Many patients are released from the hospital following several days or weeks of treatment and continue to experience organ dysfunction during the ensuing years of recovery. Following the 2003 heat wave in France, mortality rates increased from 58% at day 28 of hospitalization (mean hospital stay was 24 days) to 71% mortality by the second year of recovery.[6] An epidemiologic study of military EHS patients showed approximately twofold increased risk for death from cardiovascular, kidney, and liver disease within 30 years of hospitalization.[321] Several of the clinical responses (hyperthermia, dehydration, kidney and liver damage) occurring during progression or shortly after heatstroke collapse are clinically recognized and treated. However, those occurring during the months and years following hospitalization are underreported. The mechanisms responsible for long-term decrements in organ function remain poorly understood.

CYTOKINES

Cytokines are a class of intercellular protein messengers released from macrophages, T and B cells, endothelial cells, astrocytes, and other cell types that mediate inflammatory reactions to disease and injury.[46,141,195,280,309] Cytokine-inducing stimuli include bacterial and viral infection,[65,243] psychologic stress,[191,234] heat stress,* whole-body hyperthermia,[222] and exercise.[38,209,224,298] The defining characteristics of cytokines include a lack of constitutive production, the ability to regulate each other's production, and overlapping actions that depend on the target cell type and cytokine milieu in which they function. Cytokines act over short distances and time spans (half-life is generally less than 60 minutes) and are usually present at low concentrations in the circulation. Cytokines bind reversibly to high-affinity cell-surface receptors and stimulate intracellular signaling pathways (e.g., NF-κB) that alter the transcription of genes involved in immune responses.

There are several lines of evidence that link cytokines with symptoms of heat-induced SIRS. These include induction of heatstroke symptoms by cytokine injection in experimental animal models, association of increased circulating cytokine levels with heatstroke morbidity/mortality, and effectiveness of cytokine neutralization in altering heatstroke mortality in animal models. Peripheral injection of IL-1β, IL-2, IL-6, IL-10, TNF-α, and platelet-activating factor into experimental animals replicates the pathophysiologic responses observed in heatstroke, including hyperthermia, hypothermia, fever, increased vascular permeability, DIC, and death.† Simultaneous injection of multiple cytokines (e.g., IL-1 and TNF) is most effective in mimicking heatstroke symptoms and has shed light on cytokine interactions in vivo that orchestrate SIRS. Increased circulating levels of IL-1α, IL-1β, IL-1 receptor antagonist (IL-1ra, a naturally occurring antagonist of IL-1), IL-6, soluble IL-6 receptor (sIL-6R), IL-8, IL-10, IL-12, IFN-γ, TNF-α, and soluble TNF receptor (sTNFR) concentrations are commonly observed at the time of heatstroke collapse or shortly after cooling.* Sustained high IL-6 levels during cooling correlate with heatstroke severity, tissue injury, and death, whereas high circulating IL-8 levels are implicated in leukocyte activation and coagulation in EHS patients.[23,125] The reciprocal regulation of IL-12 and IL-10 production suggests complex interactions in heat-induced SIRS, but the function of these cytokines has not been clearly delineated. As previously mentioned, high IFN-inducible gene expression and IFN-γ levels are clinical measures of viral or intracellular bacterial infection and are evident in EHS patients with preexisting infections.[289]

The failure of clinical and animal studies to correlate cytokine production with specific heatstroke responses is probably caused by the short half-life of these proteins, local tissue concentrations exceeding those in the circulation, or the presence of soluble cytokine receptors that mask detection or alter cytokine action(s).† For example, the sTNFR inhibits the actions of TNF and is often higher in heatstroke survivors than nonsurvivors, suggesting that TNF may mediate lethality.[109] On the other hand, the sIL-6R may potentiate endogenous IL-6 effects by increasing the concentration of available IL-6 signaling receptors on cell membranes (known as a trans-signaling effect) or reduce IL-6 signaling through competitive binding with IL-6 receptors that are already present on the cell membrane (Figure 10-9).

Although cytokines are known to interact with one another, their soluble receptors, and other endogenous stress hormones (e.g., glucocorticoids) during SIRS, it remains unknown how these interactions in vivo affect heatstroke outcome. Taken together, results from the few antagonism/neutralization studies that have been conducted to date indicate that high levels of cytokines may be detrimental for heatstroke recovery, but baseline (permissive) actions of some cytokines (e.g., IL-6, TNF, or proteins affected by their actions) appear to be essential for survival.[170] Clearly, more research is required in this area to determine the multitude of cytokine actions in heat-induced SIRS and determine the protective versus detrimental effects of the proteins on multiorgan system function.

HEAT SHOCK PROTEINS

Heat shock proteins (HSPs) are molecular chaperones that prevent misfolding and aggregation of cellular proteins during exposure to stressful stimuli.[76,111,134,184] HSPs are found in organisms ranging from bacteria to humans. Their chaperonin activities protect against environmental (heavy metals, heat stress), physiologic (cell differentiation, protein translation), and pathologic (infections, ischemia/reperfusion) stimuli that cause cellular damage.[134,160,184] HSPs were originally discovered in *Drosophila melanogaster,* when puffs associated with novel protein synthesis appeared on the giant chromosomes of the salivary glands in response to heat stress.[259,303] It was later discovered that heat denaturation of mature proteins inside the cell was the cellular signal that increased protein synthesis in response to heat stress in *Drosophila.*[120]

HSPs are grouped into families according to their molecular mass, cellular localization, and function (Table 10-6).

HSP 27 (also referred to as sHSP) is a constitutively expressed cytosolic and nuclear protein with cytoskeletal stabilization and apoptotic functions.[7,167,241] HSP 60 exists in the mitochondria and cytosol, is released from PBMCs upon LPS stimulation, and functions as a "danger" signal for the innate immune system. HSPs interact with PAMPs, such as TLRs, to stimulate monocytes, macrophages, and dendritic cells to produce cytokines.[35,226] The HSP 70 family has been extensively studied for protective function(s) against thermal stress,[142,340] ischemia/reperfusion,[196,248,293] tissue

*References 20, 27, 36, 116, 172, 181.
†References 154, 162, 168, 169, 235, 237, 277, 306.

*References 20, 26, 27, 109, 112, 172.
†References 2, 20, 23, 26, 109, 112, 159, 275.

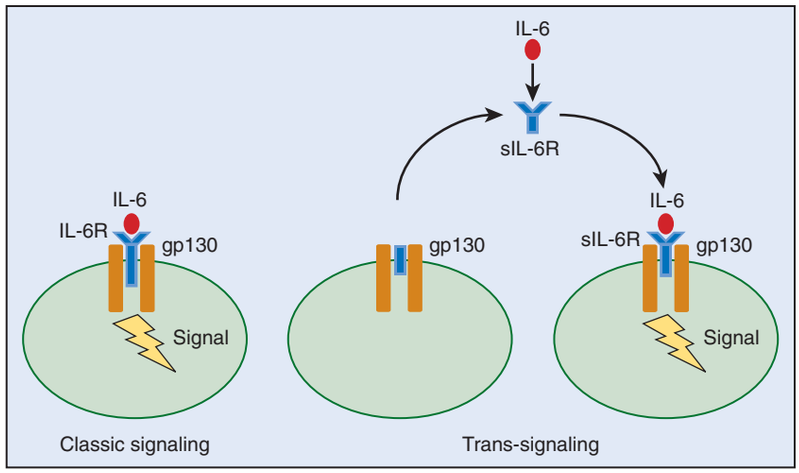

FIGURE 10-9 IL-6 receptor signaling pathways. Classic signaling involves binding of IL-6 to the membrane bound IL-6 receptor (IL-6R), which stimulates an interaction between the IL-6:IL-6R complex and the membrane-bound glycoprotein 130 (gp130) to initiate intracellular signaling. Trans-signaling occurs when the extracellular domain of the membrane-bound IL-6R is proteolytically cleaved, leading to generation of the soluble IL-6R (sIL-6R) that binds IL-6. The IL-6:sIL-6R complex can stimulate cells that only express gp130 (i.e., do not normally possess the transmembrane IL-6R) to transmit an intracellular signal. Cells that express gp130 only would not be able to respond to IL-6 in the absence of sIL-6R.

injury,[33] glucose deprivation,[334] and sepsis.[166,317] HSP 70s function in concert with other molecular chaperones, such as HSP 90 and HSP 110, to facilitate LPS and antitumor responses.[127]

HSP gene expression is mediated primarily at the level of gene transcription by a family of heat shock transcription factors (HSFs) that interact with the heat shock regulatory element (HSE) in the promoter region of genes. HSF-1 is the major stress responsive element in mammalian cells that is activated by febrile-range temperatures.[318,338] HSF-1 interacts with HSEs on cytokine genes to alter transcription and confer protection against endotoxin and other infectious/inflammatory stimuli. In gene-transfected human PBMCs, inhibition of TNF-α, IL-1β, IL-10, and IL-12 in response to LPS was specific to HSP 70 overexpression.[59] A lack of effect of HSP 70 on IL-6 gene transcription may be an indirect mechanism of protection, because IL-6 functions in a regulatory feedback loop to inhibit IL-1 and TNF production, which are Th1 cytokines with potent proinflammatory activities.[59,71,73,325] In murine macrophages, HSP 70 inhibited IL-12 (Th1) and stimulated IL-10 (Th2) production in response to LPS.[325] The shift from Th1 to Th2 cytokine production may be a mechanism by which HSP 70 protects against bacterial infection.

TABLE 10-6 Heat Shock Protein Structure and Function

Family	Function	Attributes
HSP 27 (sHSP)	Antiapoptotic,	Constitutively expressed
	Cytoskeletal stabilization	Cytosolic and nuclear
HSP 60	Protein refolding Prevents aggregation of denatured proteins Immune responses	Mitochondria and cytosol
HSP 70 family		
HSP 72	Thermotolerance	Highly inducible
HSP 73 (HSC 70)	Molecular chaperone	Constitutively expressed
HSP 75	Molecular chaperone	Mitochondrial
HSP 78 (GRP 79, Bip)	Cytoprotection	Endoplasmic reticulum
HSP 90 family: HSP 90		
GRP 96	Glucocorticoid receptor functioning Glucose regulation	Cytosolic and nuclear Endoplasmic reticulum
HSP 110/104	Molecular chaperone Tumor antigen presentation	Cytosolic

40 *Bip, GRP, HSC, HSP,* heat shock protein.

Data from Hartl FU, Hayer-Hartl M: Molecular chaperones in the cytosol: From nascent chain to folded protein. *Science* 295:1852, 2002; and Kregel KC: Heat shock proteins: Modifying factors in physiological stress responses and acquired thermotolerance. *J Appl Physiol* 92:2177, 2002.

Heat strain is a consequence of the time and intensity of heat exposure. These factors interact in vivo to influence the magnitude and kinetics of HSP expression. In human PBMCs, maximal expression of intracellular HSP 70 was observed between 4 and 6 hours after a brief heat shock (43° C [109.4° F] for 20 minutes).[288] Increased expression of HSP 10, 20, 40, 60, 70, 90, and 110 was observed in PBMCs from EHS patients or following exposure to hypoxia in vitro.[287,289] Anatomic differences in the magnitude and kinetics of in vivo expression have also been observed, with HSP 70 expression occurring within 1 hour in the brain, lung, and skin and delayed until 6 hours after heat exposure in the liver of rats.[18] In mice, liver expression of HSP 70 showed a progressive increase from approximately 6 to 24 hours following collapse from passive heatstroke.[171] In rats, a high rate of passive heating (0.175° C [0.315° F]/min) induced greater HSP 70 expression in the liver, small intestine, and kidney than did a lower rate of heating (0.05° C [0.09° F]/min), despite attaining the same maximum body temperature (42° C [107.6° F]).[80] Differences in tissue blood flow and metabolic activity likely account for regional differences in HSP expression during passive and exertional heat exposure.

Thermotolerance is the term used to describe the noninheritable, transient resistance to a lethal heat stress that is acquired following previous exposure to a nonlethal level of heat stress. Increased HSP 70 expression is a mechanism of thermotolerance that protects against heat-induced increases in epithelial permeability. A unique in vitro model system consisting of high-resistance Madin-Darby canine kidney (MDCK) epithelial cell monolayers was developed to examine the relationship between HSP 70 expression and changes in epithelial integrity with heat exposure. Following heat stress to 38.3° C (100.9° F), MDCK monolayers showed an increase in permeability that was reversible with cooling.[212] If the monolayers were preexposed to a conditioning heat stress of 42° C (107.6° F) for 90 minutes, subsequent exposure to a higher temperature of 39.4° C (102.9° F) was required to increase monolayer permeability.[21] The association of a thermotolerant state with increased HSP 70 expression suggests that HSPs shift the temperature threshold upward to prevent heat-induced disruptions in epithelial permeability.[212] Follow-on studies showed that HSPs interact with proteins in the tight junctions of the epithelium to regulate permeability. Occludin is a plasma-membrane protein located at tight junctions that was increased, along with HSP 27, 40, 70, and 90, in intestinal epithelial monolayer (Caco-2) cells exposed to 39° or 41° C (102.2° or 105.8° F).[60] Treatment of Caco-2 cells with quercetin (an inhibitor of HSF-1) inhibited HSP and occludin expression and reversed the thermotolerant state of these cells.[60] These studies demonstrate a complex interaction between HSPs and tight-junction proteins for modulation of epithelial barrier function during thermal stress.

It is interestingly to speculate that differences in HSP expression profiles may be a sensitive marker of heat stress susceptibility among different populations. During the life of an organism, there is an accumulation of protein damage caused by continual oxidant and free radical activity within cells. The lifespan of *Drosophila* was extended by heat shock treatment or the addition of HSP 70 gene copies, suggesting that increased protein chaperonin activity may protect against aging.[148,301] In rats, aging was associated with a significant reduction in liver HSP expression following passive heat exposure, which was associated with greater liver damage compared with that observed in young rats.[161,342] Older animals do not appear to have a global inability to express HSP, because exertional heat stress can induce expression profiles similar to that of mature rats.[161] Rather, aging is associated with a reduction in the threshold for HSP stimulation.[161] Similarly, Fargnoli and co-workers[72] showed that global reduction in protein synthesis was not responsible for decreased HSP induction in aged lung fibroblasts. Alzheimer's disease is thought to be a consequence of decreased HSP function that results in increased deposition of abnormally folded proteins.[211] It is anticipated that screening for altered HSP titers will help to identify individuals with reduced thermotolerance caused by aging, infection, or other conditions that may predispose to heatstroke.[150]

Heatstroke Treatments (See Chapter ••)

Current heatstroke therapies fall into two categories: supportive therapies directed at the immediate clinical symptoms and therapies directed at the causative mechanisms of injury. The primary objectives of clinical heatstroke treatments are to reduce body temperature as rapidly as possible, reestablish normal CNS function, and stabilize peripheral multiorgan system function. Supportive therapies consist of rapid cooling and IV fluid administration for restoration of normal blood pressure and tissue perfusion, whereas advanced therapies are directed at the coagulation and inflammatory disturbances that cause organ failure. Despite these efforts, heatstroke morbidity and mortality rates remain quite high, and multiorgan system dysfunction continues to claim the lives of heatstroke victims during ensuing years of recovery.[6,321] This section discusses conventional clinical treatments of heatstroke, as well as innovative treatment strategies targeted at SIRS to mitigate injury and death.

COOLING

Rapid cooling is considered the single most important treatment for protection against permanent CNS damage and death from heatstroke. To facilitate cooling, the individual should be placed into a supine position and as many clothes as possible removed to expose a large surface area of the body to facilitate heat transfer. If the individual is comatose, he or she should be placed onto his or her side to ensure an open airway. Conventional methods of cooling include cold or ice water immersion, packing ice around the body, sponging with (or without) fanning, or use of a hypothermic blanket. The goal of all cooling methods is to rapidly decrease and maintain body temperature below 39° C (102.2° F) and to prevent rebound hyperthermia. The use of an ice bath or ice packs on the skin surface has met with some resistance because it is thought that cooling of the skin will elicit peripheral vasoconstriction and shivering, which can increase heat production and counteract the cooling effect. This was shown in an experimental study in which young, fit test subjects were heat stressed to 40° C (104° F) and experienced shivering and cold sensations during immersion in cold water.[339] Because the threshold for activation of shivering is increased in heatstroke patients, the risk for cold or ice water immersion eliciting such a response and compromising the benefits of cooling is unlikely. However, to minimize the possibility of peripheral vasoconstriction with cooling, the skin may be massaged to stimulate increases in cutaneous blood flow. Regardless of the treatment strategy, current medical doctrine dictates that heatstroke patients are cooled as rapidly as possible until normal CNS function is reestablished.

Dantrolene and nonsteroidal antiinflammatory drugs (NSAIDs) have been tested for their effects on body cooling, but neither class of drugs has shown efficacy for protection against heatstroke. Dantrolene is a calcium-lowering agent that protects against hyperthermia by lowering intracellular calcium concentrations in skeletal muscle to decrease muscle tone. Dantrolene is effective for the treatment of malignant hyperthermia (MH), which is a genetic mutation that predisposes to involuntary muscle contractions and rigidity following exposure to general anesthetics or muscle-depolarizing agents. Dantrolene has been considered as a treatment for heatstroke, but animal and human heatstroke studies have failed to validate its use for this condition. In a study of heatstroke patients, dantrolene decreased the required cooling time by approximately 20 minutes but had no effect on recovery. Similarly, a randomized, double-blind, placebo-controlled trial of Hajj heatstroke patients failed to show a cooling advantage of dantrolene over traditional cooling methods.[22,43] MH is distinct from exertional or passive heatstroke, so it is not surprising that this drug does not protect equally against these diverse conditions. (MH is discussed in detail later in this chapter.)

NSAIDs have been considered as therapeutics based on their potent antiinflammatory and antipyretic effects. The action(s) of classic NSAIDs, such as, aspirin, ibuprofen, and acetaminophen, are attributed primarily to blockade of the cyclooxygenase (COX) pathway of eicosanoid metabolism (Figure 10-10).

Prostaglandins are synthesized by the COX pathway in response to a variety of stimuli (e.g., bacterial infection, heat shock) and regulate a multitude of physiologic responses, including fever, inflammation, and cytokine production. During fever, prostaglandins are released in response to proinflammatory cytokines (e.g., IL-1, IL-6) and stimulate an increase in the temperature set point to induce fever.[292] Inhibition of prostaglandin production by NSAIDs is the primary mechanism for the antipyretic (i.e., fever-reducing) actions of these drugs. However, hyperthermia in response to heat exposure is not caused by an increase in the temperature set point but by an unregulated increase in body temperature that occurs when heat gain exceeds heat loss in an absence of a change in the temperature set point (see Figure 10-4). Rather than providing a beneficial effect, NSAIDs are contraindicated as a treatment for heatstroke because of the potential toxic effects of these drugs on liver function and a lack of clinical and/or experimental data to support their use. For example, pretreatment with sodium salicylate was without effect on skin temperature and pulse rate but significantly increased the rate of body temperature rise and potentiated hyperthermia in men walking in a hot environment.[135] As previously mentioned, the use of antipyretic drugs, such as acetaminophen, has been anecdotally associated with the need for liver transplantation.[93,113,114,269,319] Recurrent hyperthermia is a common

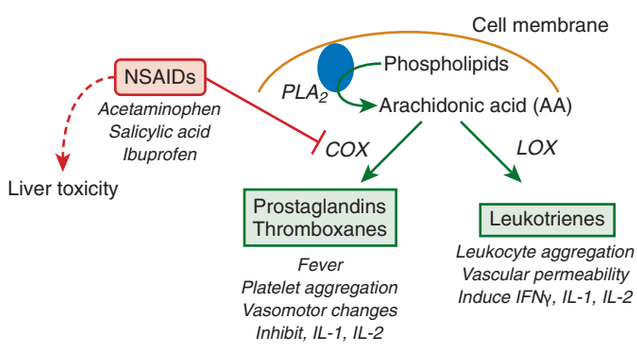

FIGURE 10-10 Eicosanoid metabolism is initiated when cell membrane phospholipids are converted to arachidonic acid (*AA*) by the enzymatic actions of phospholipase A_2 (*PLA_2*). Cyclooxygenase (*COX*) converts AA to prostaglandins and thromboxane, whereas the lipoxygenase (*LOX*) pathway is responsible for the production of leukotrienes. Nonsteroidal antiinflammatory drugs (*NSAIDs*) block the action of COX enzymes with potential toxic effects on the liver. *IFNγ,* Interferon-γ; *IL-1,* interleukin-1; *IL-2,* interleukin-2.

heatstroke recovery response that is thought to be a true fever and a prostaglandin-mediated response to endotoxin leakage and cytokine stimulation. Whether the effects of NSAIDs on cytokine expression or body temperature will protect or exacerbate the heatstroke sequelae in vivo is unknown but is an important area of investigation, given the high use of NSAIDs as over-the-counter medications for pain and/or fever relief in our society.

17 FLUID RESUSCITATION (See Chapter ••)

One of the first lines of defense against permanent tissue damage is treatment with resuscitation fluids. The objective of IV fluid administration is to restore intravascular volume and rehydrate the interstitium to stabilize cardiovascular functioning, improve tissue perfusion, and maintain immune function. The resuscitation fluid needs to be safe, efficacious, inexpensive, easy to transport for use in military or athletic settings, and have the capacity to restore tissue oxygen perfusion and minimize cellular/tissue injury. Blood provides oxygen-carrying capacity and volume, but supply is limited and there is a risk for allergic or infectious reactions, difficulties with crossmatching, and potential for high hemoglobin levels to increase blood viscosity and reduce nutrient flow to the tissues.[255,258] Balanced salt solutions, such as saline and lactated Ringer's, have a long shelf life and are inexpensive and in unlimited supply with a minimal risk for disease transmission. However, they are able to freely cross semipermeable capillary membranes, which increases the risk for tissue edema and makes frequent transfusions necessary to maintain adequate plasma volume.[110,145,304] Tissue edema increases the distance from blood vessels to tissue mitochondria and limits oxygen delivery to the tissues. There is a greater risk for edema in heatstroke patients because of increases in capillary permeability and lack of muscle movement that limits the flow of lymph following collapse.

To minimize the adverse consequences of balanced salt solutions, these fluids may be replaced with colloid solutions. Natural colloids, such as albumin, possess antioxidant properties that reduce tissue injury during times of oxidant stress but carry a risk for infection.[84,328] Dextran is an artificial colloid that was in use after World War II until adverse hemostatic effects restricted its use to specific clinical conditions, such as venous thrombosis and pulmonary embolism.[15,55] Hydroxyethyl starch (HES) is a blood plasma substitute that exerts high colloidal pressure to stimulate movement of fluid from the interstitial space into the blood vessel lumen for plasma volume expansion.[239,336,344] Small-volume treatment with HES protected against heatstroke mortality in rats, but use of HES in other heatstroke animal models and humans has not been validated.[187] Because of severe dehydration and acute renal failure with heatstroke, fluid shifts from the interstitial fluid into the vessel lumen may mean HES will not be well tolerated in severe heatstroke patients.

ANTICOAGULANTS

Anticoagulants (e.g., heparin, aspirin) have been examined for heatstroke protection, with mixed results. Heparin therapy has been associated with positive heatstroke outcome in patients, although it is difficult to dissociate the direct effects of this therapy from other clinical treatments.[245,290] The mechanisms of heat-induced DIC may include prostaglandin synthesis, because aspirin has shown protection against platelet hyperaggregation in vitro and in animal models. In human volunteers, the ingestion of aspirin 12 to15 hours before blood sampling or heat exposure of cells was effective in inhibiting platelet hyperaggregation.[87] However, aspirin was ineffective if provided after heat exposure, even though complete inhibition of the arachidonic acid pathway was achieved.[87] The ability of aspirin to protect guinea pigs from DIC induced by *Staphylococcus aureus* suggests that similar activities function in vivo to control platelet reactivity.[227] However, there is currently insufficient evidence to support the use of aspirin as a preventive measure in heatstroke patients. Given the hormonal and metabolic alterations that accompany heatstroke, including dehydration, increased catecholamine levels, hypoxia, and others, the mechanisms responsible for DIC extend beyond those mediated by prostaglandins alone. Furthermore, aspirin and other antiinflammatory drugs can cause liver damage if consumed in large quantities, as previously mentioned.

Recombinant APC is an effective antiinflammatory drug for the treatment of sepsis and may also hold promise as a treatment for heatstroke patients. APC efficacy appears to depend on a variety of patient conditions, including age (most effective in patients over 50 years of age), extent of organ dysfunction (benefit not apparent if failure of only one organ), and the presence of shock at the time of infusion, which improves its efficacy.[327] In rat heatstroke models, the efficacy of APC depends on the time of treatment. A single dose of recombinant human APC provided at the onset of heatstroke inhibited inflammation and coagulopathy, prevented organ failure, and improved survival; however, if treatment was delayed for 40 minutes following the onset of heatstroke, there was no beneficial effect on survival time.[45] The efficacy of APC was less obvious in a baboon heatstroke model. Infusion for 12 hours following heatstroke onset attenuated plasma IL-6, thrombomodulin, and procoagulant components but had no effect on mortality.[25] APC is the first biologic agent approved in the United States for the treatment of severe sepsis on account of two decades of research in this area,[327] but there is insufficient evidence to justify the use of this treatment in heatstroke patients.

ANTICYTOKINE THERAPIES

As previously described, attenuations in splanchnic blood flow during heatstroke contribute to increased gut permeability and a rise in circulating endotoxin. This series of events is hypothesized to stimulate elevations in plasma cytokine levels that have been implicated in the adverse consequences of SIRS. Based on these findings, the question arises: Do anticytokine therapies represent an efficacious treatment strategy for heatstroke? There have been no controlled studies examining the efficacy of anticytokine therapies on patient outcome with heatstroke. However, clinical trials of sepsis indicate that potential protective effects of anticytokine therapies need to be viewed with cautious optimism. Sepsis patients display high circulating IL-1 levels that correlate with morbidity and mortality, but IL-1ra treatment has been unsuccessful in reducing mortality.[236,253] A comparison of 12 randomized, double-blind multicenter trials of more than 6200 sepsis patients showed no significant benefit of antiendotoxin antibodies, ibuprofen, plasminogen-activating factor receptor antagonist, anti-TNF monoclonal antibody, or IL-1ra on all-cause mortality.[57] There are several explanations for negative results from anticytokine therapies, including the possibility that the mediator has no pathophysiologic role in the response, the agent failed to neutralize the protein (because of a lack of biologic activity, competition by other mediators, inadequate anatomic distribution), compensatory increase of other mediator(s) with similar activities, administration too early or late in the course of disease, too-short therapy duration, or the need for combination therapy.[198] Kinetic studies have shown the half-life of IL-1ra to be approximately 20 minutes, and Phase III clinical trials showed that circulating IL-1β levels at the time of clinical treatment were undetectable in 95% of the patient population.[77,246] Exposure to anticytokine therapies before sepsis onset is thought to be desirable (but practically infeasible), although this may suppress shifts in Th1/Th2 immune responses that are important for the resolution of infection. On the other hand, anticytokine therapies given too late in sepsis progression may shift the Th1/Th2 milieu in an unpredictable manner or have no effect because of the overwhelming nature of the septic event.[100] The transient nature of cytokine production and/or clearance and lack of correlation between serum levels and disease severity further complicate treatment scenarios. Given the short half-life of TNF-α (approximately 6 to 7 minutes)[16] and biphasic clearance patterns of IL-1β and IL-6 (rapid disappearance in the first 3 minutes followed by an attenuated clearance over the next 1 to 4 hours),[152] the narrow protective window in which anticytokine therapies may be effective is a difficult obstacle to overcome.

Interleukin-10 is a potent antiinflammatory cytokine that suppresses the production of several proinflammatory cytokines, including IL-1β, IL-6, and TNF-α and is an important negative feedback loop during infection/disease.[101,311] Few, if any, studies

have investigated the efficacy of IL-10 treatment for heatstroke recovery, although the cytokine has been commonly used in the treatment of multiple autoimmune diseases, including rheumatoid arthritis, Crohn's disease, multiple sclerosis, and sepsis.[31,229] As with other cytokines, the timing of IL-10 administration must be carefully considered. IL-10 decreases IFN-γ production by natural killer and Th1 cells, which may suppress the clearance of infectious organisms (via IFN-γ).[254,320] Consistent with anticytokine therapies, the beneficial effects of exogenous IL-10 administration depend upon multiple factors, including time of administration, route, and the site to which the cytokine is targeted.[229,265] These considerations, along with the immune suppressive and unpredictable nature of IL-10–based therapies, have resulted in diminished enthusiasm for anticytokine therapies for sepsis.

Heatstroke Prevention

Heatstroke is currently a more preventable than treatable disease. The most effective preventive measures include acclimatization to the heat, reduction in the duration and extent of physical activity, rescheduling of activities to cooler times of the day, increased consumption of nonalcoholic fluids, and removing vulnerable populations, such as those with preexisting viral or bacterial infections, from the heat stress environment. Fan cooling has not shown protection against heatstroke and is associated with increased thermal discomfort at temperatures above 38° C (100.4° F).[149]

HEAT ACCLIMATIZATION

Climatic heat stress and exercise interact synergistically to increase body temperature (core and skin) and cardiovascular strain and to decrease performance in the heat. Heat acclimatization is the within-lifetime changes in an organism (as opposed to evolutionary changes) that protect against these negative effects of heat strain. Heat acclimatization occurs following exposure to the natural environment, whereas heat acclimation develops following exposure to artificial conditions. However, these terms are used interchangeably because they induce similar physiologic adaptations.[331] Heat acclimation occurs following repeated bouts of heat exposure that are of sufficient intensity, frequency, duration, and number to elevate core and skin temperature and induce profuse sweating. Heat acclimation may be achieved following exercise or rest in the heat, although the former method is more effective. It is important to note that heat acclimatization is specific to the climate and activity level; therefore, if individuals will be working in a hot, humid climate, heat acclimatization should be conducted under similar conditions (Box 10-1).

Although heat acclimation does not require daily exposure to heat and exercise, the rapidity with which biological adaptations are achieved is slower with less frequent exposures. This was shown experimentally in human volunteers in whom heat acclimation was achieved following 10 days of daily heat exposure but required 27 days when the frequency of exposure was reduced to every third day of experimentation (conditions 47° C (116.6° F), 17% relative humidity).[74] Continual 24-hour exposures are also not required, because daily 100-minute periods of exposure were adequate to produce heat acclimation in subjects exposed to dry heat.[183] However, because of the transient nature of the biological adaptations, continued heat exposures are required to maintain the acclimated state. Aerobically trained athletes retain heat acclimation benefits longer than do unfit individuals, because they are exposed to high body temperatures during training exercises.[240]

Improvements in thermal comfort and exercise performance are achieved in heat-acclimated individuals through a variety of physiologic mechanisms, including a lower threshold and higher rate of skin blood flow, reduction in metabolic rate, earlier onset and rate of sweating, and improvements in cardiovascular function and fluid balance.[271] *Figure 10-11, online* illustrates the effect of 10 days of heat acclimation on heart rate, core temperature, and mean skin temperature responses of subjects walking on a treadmill in a desert type of environment.[69]

BOX 10-1 Heat Acclimation Strategies

Must Mimic Climate of Athletic Event or Occupational Setting and Include Adequate Heat Stress

- Heat must be sufficient to cause heavy sweating.
- Use exercise/rest cycles to intensify or diminish the effect of the heat stress on bodily functions.
- Include at least 6 to 14 days of adequate heat stress.
- Exercise daily for at least 90 minutes.

Start With Acclimation and Exercise Training

- Be flexible in scheduling training.
- Build confidence.
- Performance benefits may take longer to achieve than physiologic benefits.

Methods of Heat Acclimation

Use a climate-controlled room (sauna or heat chamber) or hot weather.

Incorporate training by including additional acclimation sessions.

Days Leading to Athletic Performance or Event

- Start slowly, and decrease training duration and intensity; limit heat exposure.
- Acclimatize in heat of the day.
- Train in coolest part of the day.
- Use appropriate work/rest cycles.
- Be vigilant of salt and fluid needs, especially during the first week of acclimation.

On the 10th day of acclimation, heart rate was lower by approximately 40 beats/min, and rectal and skin temperatures were reduced approximately 1° C (1.8° F) and 1.5° C (2.7° F), respectively (see Figure 10-11).[69] Once heat acclimation is achieved, skin vasodilation and sweating are initiated at a lower core temperature threshold, and higher sweat rates can be sustained without the sweat glands becoming "fatigued."[52,81] Whereas an unacclimated individual will secrete sweat with a sodium concentration of approximately 60 mEq/L (or higher), the concentration of secreted sodium from the sweat glands of an acclimated individual is significantly lower at approximately 5 mEq/L.[262] This effect of heat acclimation on salt conservation is thought to be caused by increased aldosterone secretion or responsiveness of the sweat glands to this steroid hormone, which is released by the adrenal cortex and increases the resorption of ions and water in the distal tubules and collecting ducts of the kidney.[82,151] Overall improvements in fluid balance with heat acclimation include reduced sweat sodium losses, a better matching of thirst to body water needs, and increased total body water and blood volume.[190,270] Provided that fluids are not restricted during physical activities, heat-acclimated individuals will be better able to maintain hydration during exercise and showed a marked reduction in "voluntary" dehydration.[13,69,271] Although there is controversy regarding the ability of heat acclimation to alter the maximum temperature that can be tolerated during exercise in the heat,[223] individuals that live or train in hot environments may experience reduced incidence of syncope (Figure 10-12).[13,96,247]

An essential cellular adaptation of heat acclimation is altered expression or reprogramming of genes that encode constitutive and stress-inducible proteins.[122] Heat acclimation is associated with down regulation of genes associated with energy metabolism, food intake, mitochondrial energy metabolism, and cellular maintenance processes and upregulation of genes that are linked with immune responsiveness.[122] The HSPs are the most extensively studied heat-inducible proteins and show faster transcriptional response and elevated cellular reserves (HSP 72 specifically) in heat-acclimated versus nonacclimated individuals.[122,123,193,200] That is, whereas nonacclimated individuals require de novo HSP 72 synthesis for cellular protection, individuals that reside in hot climates maintain elevated HSP 72 levels.[190] The cellular

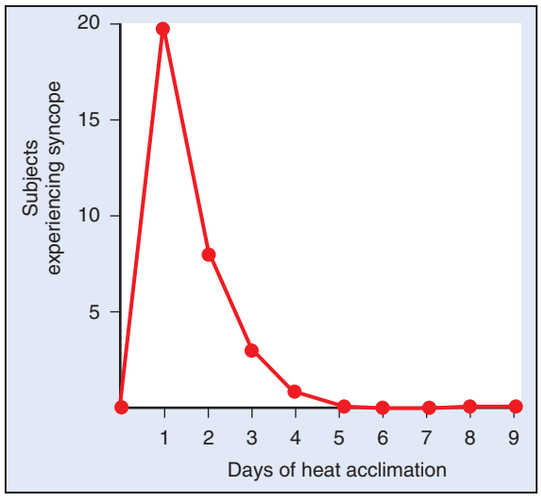

FIGURE 10-12 Incidence of syncope among 45 subjects who lived in and trained at cool ambient temperatures and could complete a physical training regimen without mishap. Then they were relocated to a hot environment where they carried out the same physical training regimen. *(Modified from Bean WB, Eichna LW:* Fed Proc *2:144, 1943, by Hubbard RW, Armstrong LE: In Pandolf KB, Sawka MN, Gonzalez RR, editors:* Human performance and environmental medicine at terrestrial extremes, *Indianapolis, 1988, Benchmark Press, pp 305-359.)*

mechanisms of heat acclimation are not fully understood but are thought to involve global and tissue-specific changes in genes involved in thermal responsiveness, DNA repair and synthesis, free radical scavenging, and apoptosis.[122]

Genetic Polymorphisms

Heatstroke susceptibility is influenced by complex interactions between environmental and host genetic factors. Emerging molecular technologies have improved our understanding of the genetic mutations and polymorphisms that may predispose to heat illness or inhibit resolution of SIRS. It is anticipated that the ability to prescreen individuals for genetic polymorphisms that may prevent resolution of SIRS will help in developing more effective therapies to alleviate morbidity/mortality in these individuals.

SINGLE NUCLEOTIDE POLYMORPHISMS

Single nucleotide polymorphisms (SNPs) are variations in the nucleotide sequence of DNA that can affect physiologic responses to environmental stimuli. SNPs have been implicated in a variety of diseases, including sepsis, type 1 diabetes, arthritis, inflammatory bowel disease, and rheumatic fever.[79,136,250,296] The identification of SNPs in the promoter region of genes suggests that disease susceptibility may be affected by altered transcription of immune determinants of clinical outcome. SNPs have been identified in IL-1, IL-2, TNF, IFNγ, IL-10, IL-1ra, TLR-2, and TLR-4. The risk for death from sepsis is significantly increased in patients with a genetic polymorphism in the TNF-α or TNF-β gene.[83] Even for those cytokine polymorphisms located distal to a critical promoter region that do not directly affect gene transcription rates, coinheritance of multiple immune-responsive genes by a process known as linkage disequilibrium can alter immune function. Some TNF-α polymorphisms exist in linkage disequilibrium with HLA haplotypes that encode cell-surface antigens. Coinheritance of these genes may ultimately be responsible for poor sepsis outcome.[138,296]

MALIGNANT HYPERTHERMIA

MH is a genetic disorder that causes muscle rigidity, hyperthermia, tachycardia, and metabolic acidosis during exposure to volatile anesthetics or depolarizing skeletal muscle relaxants. Exercise, heat stress, and emotional stress also trigger reactions in approximately 5% to 10% of MH patients.[58,326] MH reactions are a result of a massive release of calcium from the type 1 ryanodine receptor (RyR1) of the sarcoplasmic reticulum, which overwhelms cellular mechanisms of calcium homeostasis and activates actin–myosin filaments to cause muscle rigidity and hyperthermia.[238] RyR1 is the most common mutation in skeletal muscle, but additional isoforms have been identified in B and T cells, thalamus, hippocampus, and heart.[163,202,300] Activation of the RyR1 by a variety of pharmacologic compounds, including caffeine, halothane, and the muscle relaxant 4-chloro-m-cresol, has led to development of an in vitro contracture test of skeletal muscle biopsies to identify MH individuals.[266,345] Dantrolene is used to treat MH reactions by lowering intracellular calcium stores, decreasing muscle metabolic activity, and preventing hyperthermia. The use of dantrolene, in combination with improved monitoring standards and early detection using the in vitro contracture test, has helped to reduce mortality rates from greater than 70% to less than 5% in MH patients.[186]

MH has been identified in several animal species, including dogs,[231] boars,[278] cats,[14] and horses,[3] but the most common experimental animal is a porcine MH model that possesses a single mutation in the skeletal muscle RyR1 gene. These animals develop the MH syndrome in response to inhalational anesthetics, exercise, heat, and other stressors.[310] Mild exercise exacerbates MH symptoms in response to anesthetics in MH pigs, suggesting that inflammatory mediators released by skeletal muscle may contribute to the MH syndrome.[310] MH patients show approximately fivefold higher expression of IL-1β when stimulated with caffeine and 4-chloro-m-cresol compared with control cells.[94] Recent development of a transgenic mouse model that overexpresses the RyR1 receptor has proven useful to study the MH/EHS link and could shed light on the role played in this syndrome by inflammatory cytokine production from skeletal muscle or other organs.[68] Association of RyR1 mutations with EHS incidence suggests that screening young, healthy individuals (i.e., athletes, military personnel) for the MH mutation could be a powerful tool to determine heatstroke susceptibility.

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Complete references used in this text are available online at www.expertconsult.com.

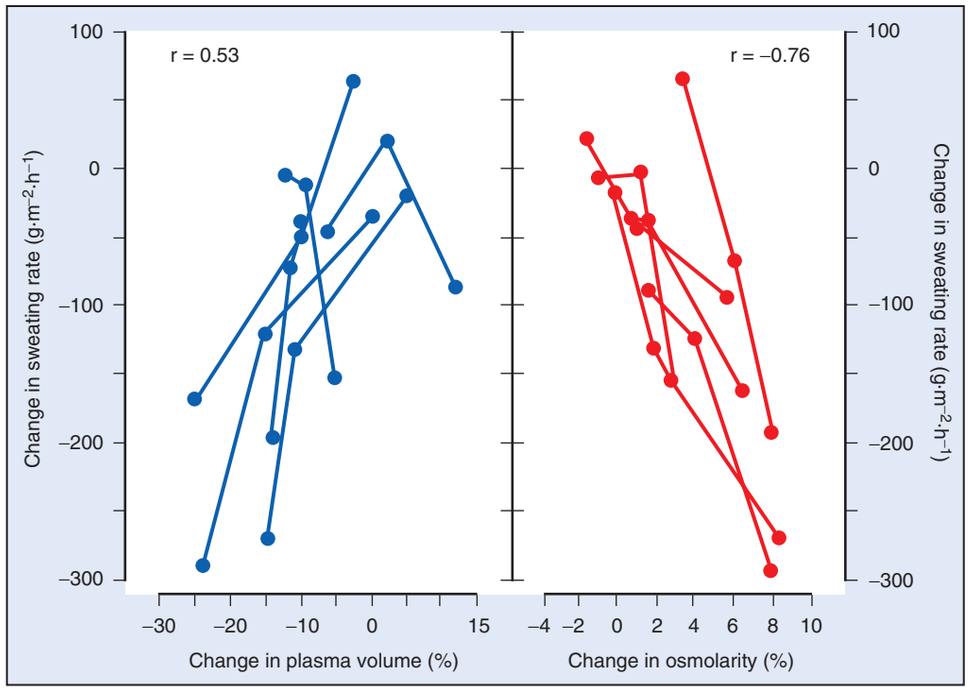

FIGURE 10-5 Effect of reduced plasma volume or increased osmolality on sweat rates in six individuals. *(Modified from Sawka MN, Young AJ, Francesconi RP, et al:* J Appl Physiol *59:1394, 1985.)*

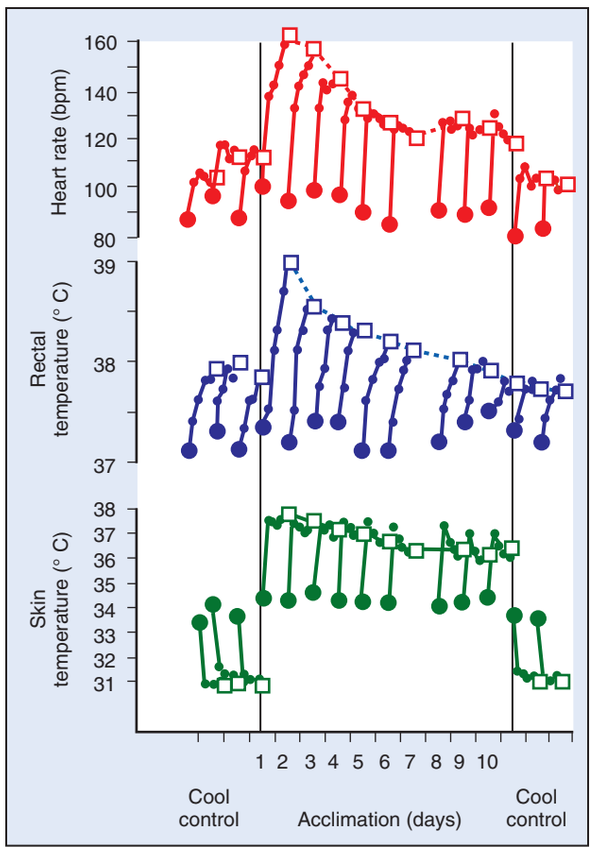

FIGURE 10-11 Effect of 10 days' acclimation on heart rate and rectal and skin temperatures during a standard exercise (five 10-minute periods of treadmill, separated by 2-minute rests) in dry heat. *Large circles*, Values before start of the first exercise period each day; *small circles*, successive values; *squares*, the final values each day. Controls of exercise in cool environment before and after acclimation. *(Modified from Eichna LW, Park CR, Nelson N, et al: Thermal regulation during acclimatization in a hot, dry (desert type) environment.* Am J Physiol *163:585, 1950.)*

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